Atherosclerotic Renal Artery Stenosis

From Causal to Incidental but not Innocent

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Dissertation University of Groningen – with summary in Dutch

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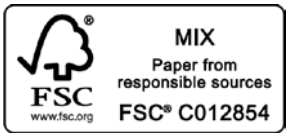

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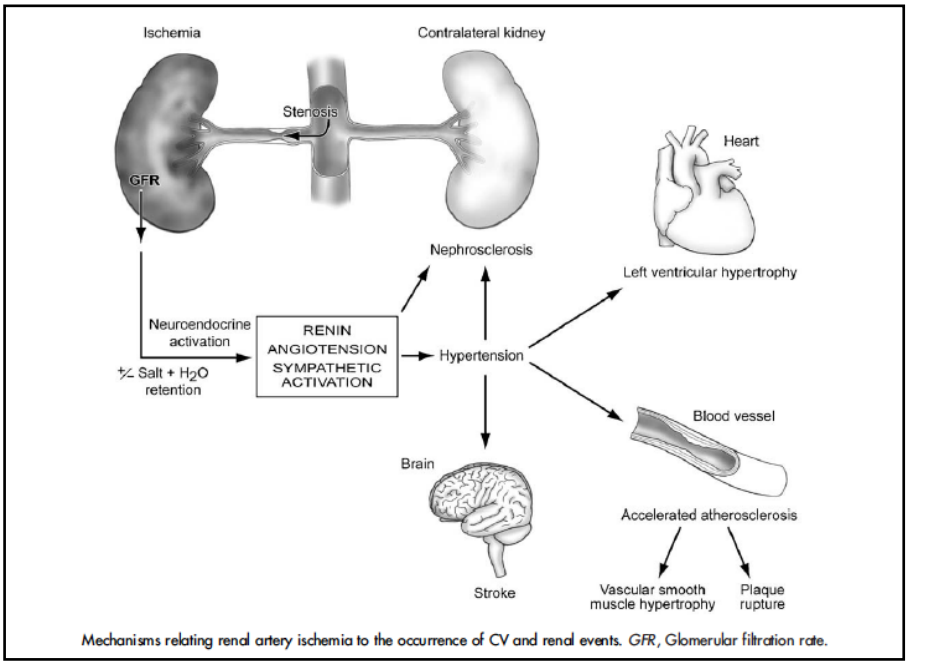
CONTENTS

Chapter 1

Introduction

Hypertension, or elevated blood pressure, is a very common risk factor for cardiovascular disease and renal end organ damage. The prevalence of hypertension is 28% in the North American countries and 44% in the European countries at the 140/90 mm Hg threshold [1]. Hypertension prevalence is strongly correlated with stroke mortality (**r**=0.78) and more modestly with total cardiovascular disease (**r**=0.44) [1]. In the vast majority of cases, no specific cause can be identified, the so-called essential hypertension. Accordingly, treatment is symptomatic, by lifestyle intervention measures and antihypertensive drugs. The lack of a causal intervention implies lifelong treatment associated with high costs and burden for the patients. In a minority of the patients a specific cause can be identified, such as primary aldosteronism, drug induced hypertension (such as due to oral contraceptives) and sleep apnea syndrome; among these, renovascular hypertension is reported to be the most frequently occurring [2, 3], with prevalence between 5% and 20% in patients referred for hypertension.

The concept of renal artery stenosis as a causal factor in hypertension derives from the classical experiments by Harry Goldblatt in the 1930s. [4-7]. He demonstrated that gross and persistent elevation of blood pressure could be produced in dogs by clamping both renal arteries or one if the other kidney had been removed. The hypertensive response to disturbed blood flow to the kidneys has since been coined the Goldblatt phenomenon, and provided the pathophysiological basis for the concept of renovascular hypertension. Many clinical and epidemiological studies showed that renal artery stenosis was associated not only with hypertension, but also with renal function loss and an increased mortality risk [8-13]. Numerous studies aimed to elucidate the specific mechanisms underlying the Goldblatt phenomenon [14, 15] and its pathogenetic role in renovascular hypertension, on short and long term and the general outline of the alleged pathogenesis is given in the figure on the next page.



Mechanisms relating renal artery ischemia to the occurrence of CV and renal events. *GFR*, Glomerular filtration rate.

In the Goldblatt concept, briefly, the renal artery stenosis leads to a downstream decrease in renal perfusion pressure that elicits a compensatory rise in activity of the renin-angiotensin-aldosterone system (RAAS) with increased renin release from the downstream kidney, as well as an increase in sympathetic nerve activity. Both lead to a rise in systemic blood pressure that aims to restore renal perfusion pressure in a homeostatic feedback loop. The elevated systemic blood pressure, however, cannot result in restoration of renal perfusion pressure due to the presence of the renal artery stenosis, thus resulting in a persistently elevated systemic blood pressure, that, on long term can result in hypertensive damage to the systemic vascular bed and to target organs, i.e. the brain, the heart and the contralateral kidney, that is not protected from the systemic hypertension by a stenotic artery. Renal artery stenosis can occur due to atherosclerosis, which is usually generalized, and due to fibromuscular dysplasia (FMD). Atherosclerotic renal artery stenosis (ARAS) is often found in patients with extrarenal atherosclerosis (5-40%), end-stage renal failure (41%) and heart failure (54%) [2], unlike FMD, which is a non-inflammatory, non-atherosclerotic disorder that leads to arterial stenosis. Among patients with renovascular hypertension, FMD accounts for 10 to 15% of cases in adults under the age of 50 years [16, 17].

As stated above, renovascular hypertension due to renal artery stenosis was reported to be the most frequently occurring secondary form of hypertension [2, 3]. Not surprisingly, much effort has been put into developing a causal treatment for renovascular hypertension, thus pursuing normalization of blood pressure and its consequent cardiorenal risk, without the burden of lifelong treatment. Studies focused on detection of renal artery stenosis in patients referred for (treatment resistant) hypertension, verification of its pathogenetic contribution to the elevated blood pressure and restoration of the patency of the renal artery. Until today, the gold standard for diagnosing renal artery stenosis is renal arteriography. A variety of less invasive tests have been evaluated for screening purposes (duplex Doppler ultrasonography, magnetic resonance angiography and computed tomographic angiography), but unfortunately false negative tests (low sensitivity) are the major concern with all noninvasive tests. Functional tests like the captopril renal scintigraphy, selective renal vein renin measurements, and plasma renin activity (in isolation or after captopril administration) can support a functional role of the renal artery stenosis in the elevated blood pressure, but are not useful as screening tests for renal artery stenosis. Eventually, the choice of test should be based upon institutional expertise and patient factors. If the noninvasive test is inconclusive, and the clinical suspicion remains high, catheter angiography is recommended [18].

With the advancement of surgical techniques in the sixties and seventies of the previous century, it became possible to reconstruct the renal artery to restore its patency [19, 20] as possible casual treatment for renovascular hypertension. However, renal artery reconstruction requires major surgery, which was associated with a substantial mortality rate (5.5%) especially in patients with diffuse atherosclerosis who also have heart failure and/or moderate to advanced renal insufficiency [21, 22]. In the eighties and nineties this was followed by percutaneous transluminal renal angioplasty (PTRA) and subsequently PTRA with stenting of the renal artery stenosis [23-26], both with the advantage of being substantially less invasive than reconstructive vascular surgery. These procedures are generally effective to improve patency of the renal artery, but had only variable success as to improvement of hypertension and renal function [24] whereas data on long-term mortality have long been lacking. Increasing experience with patency restoration gradually demonstrated that clinical benefit for blood pressure and sometimes renal function was generally readily apparent for patients with renal artery stenosis due to FMD [16, 17],

whereas for patients with ARAS the clinical benefits were much more variable [26].

The variability in clinical benefit of patency restoration raised the question whether the effect of renal artery patency interventions on blood pressure and renal function in a given individual with ARAS can be predicted from clinical parameters. In ***chapter 2,*** therefore***,*** we review the past and current literature on atherosclerotic renovascular disease and renal impairment as regards the question whether the effect of intervention aimed at restoration of patency of the renal artery, as a possibly causal treatment, can be predicted. In ***chapter 3*** we examine the relationship between success of angioplasty on patency of the renal artery on short term and during follow-up, and the blood pressure response in a single center cohort of patients with ARAS.

Next to the surgical and radiological treatment of renal artery stenosis aimed at patency restoration, the development of drugs blocking the RAAS, such as angiotensin–converting-enzyme inhibitors (ACE-i) followed by angiotensin-II receptor blockers (ARB) provided pharmacological strategies to 'regulate and intervene' in the RAAS. Early after the introduction of ACE-i this was considered particularly suited for the treatment of renovascular hypertension: after all, it was the RAAS that was held responsible for the deleterious effect of renal artery stenosis on blood pressure. Whereas RAAS-blockade turned out to be a potent strategy for blood pressure reduction in severe hypertension, nevertheless enthusiasm for its use in renovascular hypertension was curbed by two main factors. First, the blood pressure response to ACE-i in patients with renovascular hypertension could vary from pronounced to absent. Moreover, RAAS-blockade exerted unwanted effects on renal function in some patients with renal artery stenosis. It turned out that the intrarenal hemodynamic effects of ACE-i can compromise renal function in a kidney with low perfusion pressure, such as in a kidney behind a renal artery stenosis [27, 28]. In line, acute renal failure can be a consequence of ACE-i therapy in patients with bilateral renal artery stenosis, or renal artery stenosis with a single functioning kidney. Nonetheless, in patients with unilateral renal artery stenosis with normal kidney function, RAAS-blockade can be a valuable treatment. ***Chapter 4*** describes the effect of monotherapy with an ACE-i (enalapril) or ARB (losartan) compared to dual blockade with combined therapy on the blood pressure response in a small group of patients with renal artery stenosis.

Angiography is nowadays a frequent procedure for the detection of coronary as well as peripheral arterial disease (PAD). Interestingly, ARAS is frequently encountered as an incidental finding in patients undergoing routine angiography for PAD [2, 29-31] or routine coronary angiography [2, 32, 33], with prevalences ranging from 5 to 40% and from 5 to 20%, respectively. To date, the impact of renal artery stenosis as a risk factor for mortality was established mainly in populations that underwent a diagnostic work-up for hypertension and/or renal failure, that is, on clinical suspicion of renovascular hypertension. The prognostic impact of incidental renal artery stenosis, to the contrary, is unknown. To examine the prognostic impact of incidental renal artery stenosis, we investigated a cohort of patients with PAD (***chapter 5***) who underwent intra-arterial digital subtraction angiography (DSA) by systematically reviewing the angiography data for incidental renal artery stenosis, and analyzing for its possible association with prognosis. In patients with PAD, mortality is high [34-36] which is not surprising considering the clustering of cardiovascular risk factors in these patients. Whether this mortality is due to an increased (peri-) operative risk related to the surgical vascular procedure or merely a representation of the high-risk profile of these patients is not known. For clinical purposes, however, it would be very relevant to know whether incidental renal artery stenosis poses a specific risk for patients in whom surgical vascular reconstruction is considered. In ***Chapter 6,*** therefore, we investigated the impact of incidental renal artery stenosis on long-term mortality as well as peri-operative mortality in patients with confirmed PAD.

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Chapter 2

Atherosclerotic renovascular disease and renal impairment: Can we predict the effect of intervention?

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Abstract

Atherosclerotic renal artery stenosis (ARAS) is associated with hypertension, ischemic nephropathy, and high cardiovascular risk. We review the data on revascularization of the renal artery by percutaneous transluminal renal angioplasty (PTRA) and pharmacological therapy. In patients with severe ARAS and poorly controlled hypertension, PTRA can improve blood pressure control. In patients with rapid renal function loss and severe ARAS, PTRA can improve short-term renal function, but there is no evidence for long-term renoprotection. Recent evidence indicates that ARAS, and incidental renal artery stenosis, considerably increases cardiovascular risk, independent of blood pressure, renal function, and prevalent risk factors. This suggests that revascularization might potentially improve overall prognosis, but no data are available currently. The high cardiovascular risk warrants aggressive pharmacological treatment to prevent progression of the generalized vascular disorder. Ongoing trials will show whether revascularization has added, long-term effects on blood pressure, renal function, and cardiovascular prognosis.

Introduction

Atherosclerotic renal artery stenosis is associated with hypertension, ischemic nephropathy, cardiovascular disease [1,2], and a twofold to fivefold increase in cardiovascular mortality [3–5]. Furthermore, ARAS is assumed to account for 5 to 15% [6], or even 25% of new cases of end-stage renal failure [7]. The exact prevalence of ARAS in the general population is unknown because many cases remain undetected. In autopsies conducted after stroke [8] and myocardial infarction [9], the prevalence of ARAS was 10.4% and 12%, respectively. In a community-based screening for cardiovascular disease and risk factors from the United States, a prevalence of 6.8% was reported in elderly patients with a mean age of 77 years [10]. Clinical studies report widely different prevalences in populations with different clinical conditions. In hypertensive patients the prevalence of ARAS is less than 1% in unselected populations, whereas it is 5% in hospital-based populations, and up to 40% in third-line referral clinics [11,12]. Among patients starting dialysis, the prevalence of ARAS was 31% in women and 22% in men [13]. Finally, ARAS is frequently encountered as an incidental finding in patients who undergo routine angiography for peripheral vascular disease or coronary artery disease; in these populations prevalence ranges from 5 to 40% [14–17,18].

The treatment of ARAS has been a matter of dispute for a long time. In ARAS, as opposed to FMD, the narrowing of the renal artery is not an isolated phenomenon, but is part of a process of generalized atherosclerosis. The Goldblatt phenomenon, which attributes the driving force of the pathophysiologic events to increased activity of the renin-angiotensin system due to perfusion impairment in the post-stenotic kidney, may reflect relatively well the pathophysiologic mechanisms in experimental models and in renal artery stenosis (RAS) due to FMD, and is substantiated by the therapeutic benefits of revascularization by PTRA or surgery in this condition [19]. However, in ARAS the narrowing of the renal artery is not an isolated phenomenon, but part of a progressive process of generalized atherosclerosis. The impact of anatomical abnormalities in the renal artery as a driving force in the elevated, multi-organ cardiovascular risk in these patients, relative to other mechanisms of end-organ damage, is uncertain. It would seem logical to aim at revascularization of the kidney, because this has the appeal of a causal intervention. Along this line of reasoning, several controlled trials demonstrated that PTRA can indeed lower

blood pressure and may prevent clinical events such as progressive renal failure [6]. The benefits and particularly the risks of intervention have not been well defined, however, and prospective randomized data that also consider long-term outcome are lacking.

On the other hand, there is increasing awareness that ARAS occurs in the context of generalized atherosclerosis. Based on current guidelines for hypertension [20,21], the high risk in patients with ARAS warrants aggressive treatment of the prevalent cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, and glycaemia) in all patients with ARAS. Possible benefits of revascularization thus should outweigh those of optimal conservative intervention, and the possible benefit should be weighed against the risks of revascularization for individual patients. However, it should also be noted that in patients with ARAS, the risk for cardiovascular morbidity and mortality is greater than explained by blood pressure alone [1] and, remarkably, the presence of RAS in itself is an independent risk factor for cardiovascular morbidity and mortality [17,18]. This raises the intriguing possibility that revascularization may contribute to improvement of overall outcome in high-risk patients, even independent of blood pressure [18,22].

In this article we provide an overview of the available data on outcome of revascularization on top of (optimal) pharmacological therapy in ARAS on blood pressure, renal function, and prevention of cardiovascular events, and address the question whether the therapeutic effect of revascularization can be predicted, in order to be able to select the patients with ARAS who are likely to benefit from revascularization.

PTRA: Effects on Blood Pressure

Two types of revascularization procedures are available currently: PTRA with or without stenting, and surgical reconstruction. PTRA is currently the first choice because it is less invasive. Randomized data in patients with ostial ARAS showed that PTRA is as effective as surgical reconstruction, and moreover, a simpler procedure [23]. A recent meta-analysis of randomized controlled trials addressed the antihypertensive effect of balloon angioplasty versus standard medical therapy in ARAS [24]. The literature search identified three published clinical randomized trials: the EMMA trial [25]; the SNRASCG trial [26]; and the DRASTIC trial [27]. Altogether there were 210 patients in the three trials with moderate to severe (≥ 50%) unilateral or bilateral ARAS and poorly controlled hypertension who were

followed for at least 3 months (longest follow-up, 12 months) after intervention. The pooled data using the 3-month follow-up values from the DRASTIC trial and the 6-month data from the two other trials showed a significantly greater decrease in both systolic and diastolic blood pressure from baseline in the angioplasty group as compared with medical therapy. The weighted mean difference between the two treatments was –7 mm Hg (95% CI: –12 to –1 mm Hg) for systolic blood pressure and –3 mm Hg (95% CI: –6 to –1 mm Hg) for diastolic blood pressure. Patients treated with balloon angioplasty (DRASTIC trial) were more likely to have patent renal arteries after 12 months (52% vs 19%; odds ratio = 4.2; 95% CI: 1.8 to 9.8), and had a significant decrease in median defined daily doses, in the EMMA trial at 6 months (P = 0.009) whereas in the DRASTIC trial at 3 months (P< 0.001). The number of antihypertensive drugs was also significantly lower in the balloon angioplasty group at both 3 and 12 months in the DRASTIC trial. This allows us to conclude that balloon angioplasty on top of standard medical therapy has a modest but significant effect on blood pressure compared to medical therapy alone. Unfortunately, to date there are no randomized studies comparing renal artery stenting to medication.

In a trial comparing PTRA plus stenting (PTRAS) to PTRA alone [28], PTRAS seemed to be a better technique than PTRA to achieve vessel patency in ostial ARAS. However, the two procedures did not differ in their effects on blood pressure outcome after 6 months of follow-up.

PTRA: Effects on Renal Function

The natural course of the rate of renal function decline in patients with ARAS is uncertain. Progression of renal failure in patients with ARAS may reflect progression in the degree of narrowing of the renal artery, progression associated with ischemic nephropathy, or both. Rimmer and Gennari [6] reviewed five reports concerning serial angiograms in 237 patients with ARAS. Progression, including worsening of existing stenosis of the renal artery or the development of contralateral RAS, was reported in 116 patients (49%) during follow-up periods of 6 to 18 months. Renal artery occlusion occurred in 28 cases (14%). In another report, the 3-year cumulative incidence of progression, defined as any detectable increase in the degree of diameter reduction affecting at least one renal artery, was 35% [29]. In a stepwise Cox proportional hazard analysis, baseline risk factors associated with progression

were a systolic blood pressure of at least 160 mm Hg, diabetes mellitus, and high-grade (≥ 60% stenosis, or occlusion) ipsilateral or contralateral stenosis [29]. Thus far, the available randomized controlled trials focused on the effect of PTRA (on top of medical therapy) versus medical therapy alone on blood pressure [25–27]. The EMMA, SNRASCG, and DRASTIC studies are summarized in Table 1. The studies separately did not show improvement of renal function.

Table 1. Effect of PTRA versus medication on renal function

Study	Intervention, number of patients, *n*, mean follow-up, *mo*	Bilateral stenosis, *n (%)*	Renal function	Baseline	Outcome (significance)
Randomized					
Plouin et al. [25]	Medication (standard), *n* = 26 (6 mo)	None	eGFR*	73.2 mL/min	+ 0.6 mL/min (NS)
	PTRA, *n* = 23			73.2 mL/min	+ 3.6 mL/min (NS)
Webster et al. [26]	Medication (standard), *n* = 14 (3–54 mo)	None	Serum creatinine	1.87 mg/dL	No change
	PTRA, *n* = 13			1.53 mg/dL	+ 0.09 mg/dL (NS)
	Medication, *n* = 16	28 (100%)		1.64 mg/dL	+ 0.04 mg/dL (NS)
	PTRA, *n* = 12			2.02 mg/dL	+ 0.11 mg/dL (NS)
van Jaarsveld et al. [27]	Medication (standard), *n* = 50 (12 mo)	24 (23%)	eGFR*	60 mL/min	62 mL/min (NS)
	PTRA, *n* = 56			67 mL/min	70 mL/min (NS)
Nonrandomized					
La Batide-Alanore et al. [30•]	PTRA, *n* = 18 (6 mo)	None	Total GFR	83 mL/min	+ 3 mL/min (NS)
			GFR stenotic kidney	32 mL/min	+ 6 mL/min ($P < 0.001$)
			GFR nonstenotic kidney	51 mL/min	- 4 mL/min ($P < 0.001$)
Beutler et al. [31]	PTRAS, stable creatinine, *n* = 26 (12 mo)	21 (33%)	Serum creatinine	1.72 mg/dL	+ 0.04 mg/dL (NS)
	PTRAS, deteriorating creatinine, *n* = 30			2.02 mg/dL	- 0.31 mg/dL ($P < 0.036$)
Roussos et al. [33]	PTRA, with deteriorating creatinine, *n* = 48 (12 mo)	11 (23%)	eGFR†	23 mL/min	+ 7 mL/min ($P = 0.072$)
	PTRA, with accelerating HT, *n* = 47	10 (21%)		37 mL/min	+ 1 mL/min (NS)
	PTRA, with renal failure + HT, *n* = 25	7 (28%)		29 mL/min	+ 2 mL/min (NS)
	PTRA, with PVD, *n* = 24	5 (21%)		29 mL/min	+ 1 mL/min (NS)

*eGFR estimated with use of Cockcroft-Gault formula (mL/min per 1.73 m²).
†eGFR estimated with abbreviated version of MDRD equation (mL/min per 1.73 m²).
eGFR—estimated glomerular filtration rate; GFR—glomerular filtration rate; HT—hypertension; NS—not significant; PTRA—percutaneous transluminal renal angioplasty; PTRAS—PTRA plus stenting; PVD—peripheral vascular disease.

Because the lack of effect might be due to the limited power of the separate studies, due to their limited size and relatively short follow-up, the previously mentioned meta-analysis [24] tried to combine the results of the three studies to see whether intervention

could actually improve renal function outcome. However, because the effect on renal function was measured in different ways, the results could not be pooled.

The fact that there was no improvement of renal function, despite anatomically successful revascularization, may be explained in several ways. First, the patients included in these studies all had relatively normal renal function (EMMA and DRASTIC studies) or only mild renal insufficiency (SNRASCG study), so any improvement could be small as well and thus difficult to detect. Second, the specific pathophysiology of renal function impairment in ARAS should be taken into account. In unilateral ARAS, glomerular filtration rate (GFR) does not reflect individual kidney function, because hyperfiltration in the normal kidney may compensate for reduced filtration in the ischemic kidney.

Moreover, renal failure may result from both ischemia of the stenotic kidney, resulting in progressive renal fibrosis and atrophy, and hypertensive nephropathy in the contralateral kidney. In the stenotic kidney, both in unilateral and bilateral RAS, chronic ischemia may eventually result in irreversible damage to the renal parenchyma, so that dilating the stenotic lesion is no more than a "cosmetic" intervention. In this respect, La Batide-Alanore *et al.* [30] evaluated split renal function (SRF, estimated by technetium ^{99m}Tc-diethylenetriamine penta-acetic acid scintigraphy) outcome after PTRA in patients with unilateral RAS (≥ 60%). They prospectively evaluated SRF and total GFR (clearance methods) after successful PTRA in 32 consecutive hypertensive patients with RAS (18 atherosclerotic and 14 with dysplastic disease) and a total GFR of at least 60 mL/min per 1.73 m^2. Six months after successful PTRA, single-kidney GFR of the stenotic kidney had increased significantly, whereas concurrently single kidney GFR of the nonstenotic kidney decreased significantly (Table 1). Thus, reversal of both the hypoperfusion of the stenotic side and the hyperperfusion of the nonstenotic side was observed, with a slight increase in total GFR as a net result. This elegant study nicely demonstrates that "early" successful revascularization of unilateral RAS (at least in patients with normal GFR) can facilitate restoration of the normal distribution of renal blood flow, and hence renal function, between the two kidneys. This presumably protects the stenotic kidney from ischemia, and the contralateral kidney from hyperfiltration that may contribute to long-term renal parenchymal damage, especially in the presence of systemic hypertension. However, it should be emphasized that randomized prospective trials are required to confirm the long-term beneficial effects of the

establishment of a new equilibrium after PTRA on prevention of further renal function deterioration.

Although randomized studies are still lacking, several nonrandomized studies showed improvement or even delay of dialysis after PTRA (with or without stenting) in patients with ARAS and severe renal dysfunction (Table 1). Beutler *et al.* [31] demonstrated that in patients with pre-stent declining renal function (an increase in serum creatinine of ≥ 20% in 12 months), PTRAS improved median serum creatinine in the first 1 year (from 2.02 mg/dL [1.5 to 3.0 mg/dL] to 1.71 mg/dL [1.4 to 2.5 mg/dL]; $P < 0.05$) and remained stable during further follow-up monitoring (12 months after stent placement). The treatment had no effect on serum creatinine levels if function had previously been stable. Similar results were reported by Korsakas *et al.* [32] in 28 patients with a serum creatinine greater than 3.33 mg/dL, and progressive loss of renal function at least 1 year before angioplasty, in whom PTRA (with or without stent) slowed significantly progression of renal failure. A favorable outcome was correlated with a lower creatinine level ($P = 0.0137$) and a more rapid prior loss of renal function (r = 0.49, $P = 0.020$) at entry. Roussos *et al.* [33] showed that patients with ARAS who were referred for angioplasty because of deteriorating renal function (mean serum creatinine: 3.66 ± 1.89 mg/dL) had a small increase in glomerular filtration rate at 3-month follow-up (from 23 ± 11 to 27 ± 14 mL/min/1.73 m^2; $P = 0.021$). Analysis with patients who had both renal function deterioration and accelerated hypertension showed improvement of glomerular filtration rate (from 25 ± 11 to 28 ± 14 mL/min/1.73 m^2; $P = 0.031$) 3 months after intervention. However, no statistically significant difference was found 1 year after angioplasty.

Several studies attempted to identify reliable predictors of renal function outcome after revascularization. Halimi *et al.* [34] reported that the effect of intervention (PTRA, n = 5; or surgery, n = 18) in a small heterogeneous group of ARAS patients was associated with pre-intervention albuminuria. On stepwise regression analysis, pre-intervention urinary albumin excretion was the only predictor of the response of renal function to intervention, with lack of improvement in albuminuric patients. This suggests that, in ARAS, albuminuria is a marker of intrarenal parenchymal damage that is not responsive to revascularization. This is in accord with data reported by Campo *et al.* [35] in 52 patients, who reported better outcome in renal function decline after PTRA in patients with proteinuria less than 1 g/day, serum creatinine less than 4 mg/dL, and low resistance index, respectively. In this study,

neither kidney size nor rapid prior renal function deterioration predicted outcome after PTRA. A high resistance index, as assessed by Doppler ultrasonography, was also found to be a predictor of worse outcome after PTRA for blood pressure and renal function in the study by Radermacher *et al.* [36] in 138 ARAS patients. Unfortunately, however, many patients with ARAS are obese and thus not easily accessible for reliable Doppler sonography; moreover, the technique is relatively observer-dependent. The finding of a small kidney size (< 8 cm) is considered a sign of renal failure, and PTRA on such small kidneys should not be undertaken, because it is unlikely that the risks outweigh the benefits—with the exception of ARAS patients entering dialysis programs. Despite small-sized (but not shrunken) kidneys, several patients could discontinue dialysis after PTRA [37]. Krijnen *et al.* [38] analyzed data from the DRASTIC study, and found that patients with bilateral stenosis benefit the most from immediate angioplasty with regard to renal function and blood pressure after 1 year of follow-up.

In summary, data on the impact of PTRA on renal function are relatively sparse, and limited mainly to short-term studies. Whereas apparently PTRA can favorably affect overall renal function, such an effect is usually absent in patients with stable renal function, or in those in whom irreversible parenchymal damage is present, as suggested by stable moderate to severe renal function impairment or albuminuria. Current data indicate that improvement of kidney function after renal vascularization (added to standard medical therapy) may be expected in patients with rapid deterioration of renal function in the year or months before intervention, in whom renal function is nevertheless still relatively well preserved at the time of intervention. In selected cases, revascularization can result in renal function improvement even in patients in whom rapid renal function deterioration is so severe as to necessitate dialysis, as shown by case reports and Korsakas *et al.* [32]. In patients with normal to mildly impaired stable renal function, especially patients with unilateral RAS, one cannot expect improvement of kidney function and the effect of revascularization for the long-term prognosis is uncertain.

PTRA: Effects on Prevention of Cardiovascular Events and Mortality

There are no randomized clinical trials evaluating the comparative effects of renal artery revascularization with medical therapy on cardiovascular morbidity and mortality in

patients with ARAS, with or without co-morbid conditions [22]. Yet, in patients with ARAS the risk for premature cardiovascular death considerably exceeds their risk for progression to end-stage renal failure. The risk is particularly elevated in patients with lower baseline renal function, which was reported to predict mortality after PTRA [39].

This elevated risk was demonstrated recently by Kalra *et al.* [1] in a large randomly selected population cohort (n = 1,085,250) and an essentially similar picture emerges for patients with incidental RAS. Leertouwer *et al.* [15] showed that during 10 years of follow-up, if left untreated, incidental RAS did not lead to end-stage renal failure or the need for renal replacement therapy. Thus, revascularization is not recommended in incidentally discovered RAS [14,15]. However, the risk of cardiovascular mortality is considerably increased, as demonstrated in a cohort of 491 patients with peripheral vascular disease, where incidental RAS was associated with an increased prevalence of not only kidney disease but also mortality (Fig. 1) [18]. Cox regression analysis showed that RAS was an independent predictor of mortality (P = 0.005), along with age, diabetes, smoking, previous myocardial infarction, and stroke. Interestingly, inclusion of RAS in the multivariate analysis abolished the effects of hypertension and renal function on mortality. Thus incidentally found RAS is a marker of poor prognosis. This is partly explained by its close association with extended cardiovascular disease, as well as with many established risk factors, such as older age [18,40], impaired renal function [18], hypertension [18,41], history of coronary artery disease [17,18,40] and diabetes [18,41]. However, in the above population with PVD, the increased risk for mortality could not be explained fully by these factors, which accords with data from patients who undergo diagnostic cardiac catheterization simultaneously with an aortography, in whom incidental RAS was an independent risk factor for mortality [17,42].

Moreover, the severity of RAS was related to mortality. Whether the independent association between (incidental) ARAS and cardiovascular mortality implicates a causal effect has not been established, but it is conceivable that neurohumoral activation from the ischemic kidney exerts unfavorable cardiovascular effects. If so, revascularization may have the potential to improve cardiovascular prognosis, even in incidental ARAS—as has been suggested for heart failure patients with ARAS [22]. Such studies, however, have not been performed. At any rate, from the point of view of their high risk profile, all patients with (incidental) ARAS should receive optimal pharmacological and supportive treatment to manage their cardiovascular risk, in compliance with current guidelines. It is known that

rigorous treatment of hypertension and strict regulation of diabetes improve cardiovascular morbidity and mortality [43–45] and that an intensive (supra-optimal) regimen of lipid-lowering statin drugs can improve prognosis in high-risk populations, especially in patients with coronary artery disease and metabolic syndrome [46,47]. It would be of interest to test such strategies in patients with ARAS.

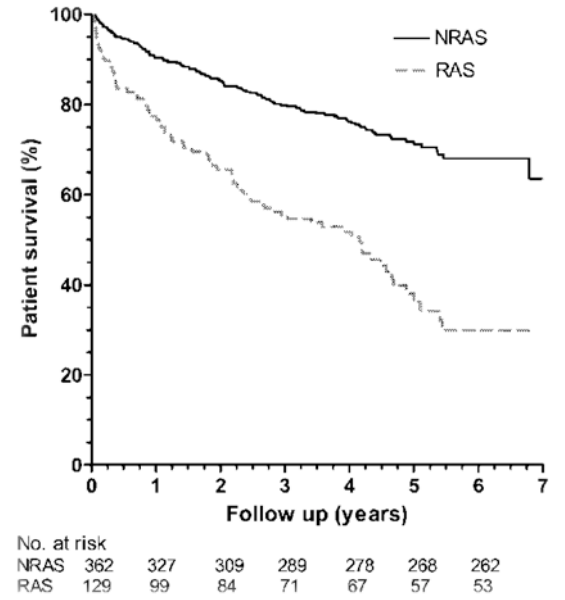

Figure 1. Kaplan-Meier survival plots for 491 patients with peripheral vascular disease, comparing outcome for those with incidentally discovered renal artery stenosis (RAS) and those without renal artery stenosis (NRAS). On Cox regression analysis the elevated risk for mortality in RAS was independent from blood pressure, renal function and other cardio-vascular risk factors.

Future Studies

Currently, four large randomized intervention trials are ongoing, with defined clinical endpoints as summarized in Table 2. The primary endpoint of the three ongoing trials from Europe is the kidney function. The STAR trial aims to compare the effects of renal artery stent placement together with optimal medication versus optimal medication alone on renal function in ARAS patients [48]. Patients are followed for 2 years with extended follow-up to 5 years. The primary outcome of this study is a reduction in creatinine clearance greater than 20% compared to baseline. This trial will include 140 patients.

The NITER trial aims to evaluate whether medical therapy plus interventional PTRAS is superior to medical therapy alone according to the following combined primary endpoint: death or dialysis initiation or reduction by greater than 20% in estimated GFR after 0.5, 1, and 2 years of follow-up and an extended follow-up until the fourth year [49]. The sample size is estimated in 50 patients per group to achieve a statistical significance of 0.05 in case of a reduction by 50% in the combined endpoints.

The ASTRAL study is the largest trial, with the intention to include 1000 patients, and compares angioplasty (with or without stenting, on top of medical therapy, free of choice) with medical therapy (free of choice) [50]. The progress of patients will be followed for at least a year. The primary comparison is the rate of progression of renal failure, as assessed by reciprocal creatinine plots over the course of the trial. Secondary endpoints include blood pressure control and the occurrence of serious vascular events (e.g., myocardial infarction and stroke).

The latest trial is from the United States, the CORAL trial [51]. Randomization will occur in 1080 patients. Optimal medical therapy alone compared to stenting with optimal medical therapy on a composite cardiovascular and renal endpoint (cardiovascular or renal death, myocardial infarction, hospitalization for congestive heart failure, stroke, doubling of serum creatinine, and need for renal replacement therapy) will be studied. Hopefully, these studies have the potential to clarify the uncertainty concerning indications for, and outcomes after, renal revascularization in patients with ARAS.

Table 2. Ongoing randomized trials with PTRAS versus medication

Randomized study	Intervention, number of intended patients, *n*, follow-up, *y*	Primary endpoint	Start study	Data available
Bax et al. [48]	PTRAS (on top of optimal medication*) vs optimal medication, *n* = 140, 2 y, extended to 5 y	Reduction in creatinine clearance > 20% compared to baseline	June 2000	Inclusion ended in 2006
Scarpioni et al. [49]	PTRAS (on top of optimal medication*) vs optimal medication, *n* = 100, 2 y, extended to 4 y	Death or dialysis initiation or reduction by > 20% in eGFR compared to baseline	January 2003	Last enrollment: January 2007
ASTRAL [50]	PTRAS (standard medication) vs medication (standard), *n* = 750 (min), 1 y, extended to 5 y	Mean slope of the reciprocal creatinine plot vs time	September 2000	Last enrollment: April 2007 (641 patients included March 2006)
Cooper et al. [51]	PTRAS (on top of optimal medication†) versus optimal medication, *n* = 1080, 2 y	Event-free survival from CV and renal adverse events	2005	Last enrollment: December 2006 (last follow-up contact: 2009)

*Optimal medication: statins, antihypertensive drugs, and antiplatelet therapy.
†Optimal medication: first-line drug angiotensin II type 1 receptor antagonist, other therapy according to JNC 7 report.
CV—cardiovascular; eGFR—estimated glomerular filtration rate; JNC 7—Seventh Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; PTRA—percutaneous transluminal renal angioplasty; PTRAS—PTRA plus stenting.

Conclusions

ARAS is a condition associated with hypertension, renal function impairment, and a particularly high cardiovascular risk. This requires optimal medical therapy aimed at treatment of the prevalent cardiac risk factors in all ARAS patients. Revascularization on top of medical therapy can improve blood pressure control in patients with severe ARAS and poorly controlled hypertension. Short-term improvement in renal function has been reported, but at this time there is no evidence that early revascularization can prevent long-term loss of renal function. However, in individuals with rapidly progressing renal function loss and severe ARAS, PTRAS can improve renal function. Recent evidence indicates that ARAS—and interestingly, incidental RAS—is associated with cardiovascular risk, also independent from blood pressure, renal function, and prevalent cardiovascular risk factors. This suggests that revascularization may have the potential to improve overall cardiovascular prognosis. Ongoing randomized trials in ARAS address the long-term effects of revascularization, on top of pharmacological intervention, on blood pressure, renal function, and mortality. It is hoped that these trials will provide us with data that can guide clinical decision making in this grim condition.

Clinical Trial Acronyms

ASTRAL—Angioplasty and Stent for Renal Artery Lesions; CORAL—Cardiovascular Outcomes in Renal Atherosclerotic Lesions; DRASTIC—Dutch Renal Artery Stenosis Intervention Cooperative; EMMA—Essai Multicentrique Medicaments vs Angioplastie; NITER—Nephropathy Ischemic Therapy; SNRASCG—Scottish and Newcastle Renal Artery Stenosis Collaborative Group; STAR—Benefit of Stent Placement and Blood Pressure and Lipid-lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery.

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Chapter 3

Lack of relationship between success of angioplasty and blood pressure response in patients with renal artery stenosis: a longitudinal follow-up by angiography

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Recently, two randomized controlled trials showed no evidence of relevant clinical benefit from revascularization in patients with atherosclerotic renal artery stenosis (ARAS) [1, 2]. One possible explanation could be restenosis, but no data are available with systematic angiographic follow-up that allow to establish the association between blood pressure effect and persistent patency of the vessel. Therefore we analyzed the radiological and clinical data of a series of 40 patients with ARAS and hypertension, who underwent an angioplasty (PTA) with protocolized repeat angiography after 1 year, irrespective of the blood pressure response.

Forty patients, 21 women and 19 men, aged 64 ± 6 years were investigated for therapy resistant and longstanding (7 years) hypertension (>140/90 mmHg on triple therapy consisting of an ACE inhibitor, β-blocker and a diuretic, or more) by means of an intra-arterial DSA. Renal artery stenosis was considered to be significant as a lumen diameter reduction more than 70%. In case of stenosis a PTA was performed. The patency of the renal artery (<50% residual stenosis after angioplasty, measured with Dinavision, quantitative angiography by Siemens, Netherlands) was re-established after 1 year with angiography (judged by a blinded radiologist, H.vdH). Blood pressure (BP) was measured by an oscillometric device (Dinamap model 8100, Critikon Inc., Fla., U.S.A.), during 30 minutes, after 1 month (short-term), and 1 year (long-term) after PTA. The hypertension was considered as improved when the SBP fell to 140 mmHg or less or DBP fell 90 mmHg or less with the same or less medication. In a total of 88 renal arteries in 40 patients, there were 60 renal artery stenoses. Twenty-four patients had a unilateral stenosis (URAS) and 16 patients had bilateral stenosis (BIRAS): of the latter seven stenoses had a diameter of less than 3 mm and were not dilated. Before intervention mean BP was 180 ± 24/98 ± 12 mmHg in the patients with URAS and 178 ± 29/95 ± 17 mmHg in the patients with BIRAS. PTA was performed in 53 arteries: 25 in URAS and 28 in bilateral lesions. No major complications occurred after PTA. Immediate patency was 96% in the URAS group (1 failure) and 75% in the BIRAS group (4 failures). The long-term patency overall was 45%, with 14 restenoses in the URAS and eight in the BIRAS group. In patients that developed restenosis after 1 year, Δ BP from baseline was -2 ± 27/1 ± 16 and -32 ± 56/-4 ± 15, respectively, in URAS and BIRAS group. In comparison, the Δ BP in patients with persistent patency was -4 ± 30/-10 ± 15 in URAS and -7 ± 28/-11 ± 18 in BIRAS group (Table 1). Neither in patients with URAS, nor in

patients with BIRAS, an association between BP response and patency was found after 1 year (URAS: χ^2 = 0.490, *p* = 0.484 and BIRAS: χ^2 = 0.291, *p*= 0.590, Table 2).

Table 1. Principal results of percutaneous transluminal angioplasty in ARAS patients

	PTA patency (immediate)	Δ BP 1-month systolic/diastolic in mmHg	PTA patency (after 1 year)	Δ BP 1-year systolic/diastolic in mmHg
URAS (n=24)	Yes: 23	-2 ± 37/-0 ± 13*	Yes: 10	-4 ± 30/-10 ± 15*
	No: 1	-39/-15	No: 14	-2 ± 27/1 ± 16
BIRAS (n=16)	Yes: 12	-8 ± 55/0 ± 21*	Yes: 8	-7 ± 28/-11 ± 18*
	No: 4	-10 ± 50/3 ± 15	No: 8	-32 ± 56/-4 ± 15

BIRAS, bilateral renal artery stenosis; PTA, percutaneous transluminal angioplasty; URAS, unilateral renal artery stenosis. Stenosis defined as lumen reduction more than 70% before PTA and patency defined as residual stenosis less than 50% after PTA. **P* = NS versus baseline.

Table 2. Association patency after 1 year and blood pressure improvement

URAS	**PTA patent**	**PTA not patent**	***BIRAS***	**PTA patent**	**PTA not patent**
BP improved	5	5		5	6
BP not improved	5	9		3	2

BP, blood pressure; PTA, percutaneous transluminal angioplasty.

In this study there was no relationship between the patency success of angioplasty and BP response at 1 year. Previous studies have shown restenosis in at least half of the patients after 6 months [3], suggesting that restenosis accounts for the return of the hypertension. Of note, repeat angiography is usually performed only when BP response is insufficient or when BP rises again. Our study is the first to report on a cohort, albeit small, where all patients underwent repeated angiography 1 year after angioplasty, irrespective of BP response, thus avoiding bias by indication. In five of the patients in URAS with restenosis, BP was improved, and in addition, in five of the patients with patent renal arteries, hypertension returned. At variance with common belief, in our patients with URAS, the relationship between patency of the renal artery and BP response is not one-to-one. For patients with BIRAS, the association between BP response and patency is more ambiguous. In our group of patients with BIRAS, there were seven stenoses not dilated because of the vessel size, so after

successful unilateral dilatation, the contralateral kidney was still underperfused, which may have caused the hypertension. Furthermore, in bilateral lesions, either kidney (or both) can be the driving force behind the hypertension, and it is impossible to determine which kidney is the culprit without invasive biochemical measurements. So, the impact of restenosis on BP cannot be assessed non-invasively in presence of a contralateral stenosis. However, the URAS data are clear-cut, and our findings support the increasing body of evidence showing that ARAS is not the main pathogenetic factor in the elevated blood pressure in the majority of ARAS patients with hypertension. ARAS may be superimposed on essential hypertension, and ARAS can also occur in the absence of hypertension, as suggested by studies in peripheral arterial disease where incidental RAS was found in about 25% of the patients [4, 5], of whom 29% were normotensive. In many patients with ARAS renal arteriolosclerosis is also present. The latter may be the main factor in renal ischemia, and can be the perpetuating factor in hypertension despite alleviation of the ARAS. These factors may explain the disappointing results of the STAR [1] and ASTRAL [2] in patients with ARAS and kidney failure, which did not show any beneficial effect of stenting, on top of medical therapy (also 18% failure of the dilating procedures, and a moderate stenosis of 50%). The limitations of our study are the small number of patients and the post-hoc design. Additionally, we did not perform stenting, which may have affected patency during follow-up. In spite of these limitations, the prospectively planned repeated angiography in all patients after 1 year provides unique data allowing to refute an association between success of patency and blood pressure effect of anatomical intervention in ARAS.

In conclusion: we could not demonstrate any relationship between anatomical effects on patency of the renal artery by PTA, and the BP response, or recurrence of the stenosis and the return of hypertension. These data cast further doubt on the concept that ARAS play a major role in causing so called renovascular hypertension. Other interventions, focusing on treatment and prevention of small artery disease rather than dilating an incidental RAS, should be explored for their therapeutic potential in hypertensive patients with ARAS.

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Chapter 4

Dual blockade of renin-angiotensin system in patients with renal artery stenosis

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Submitted

Abstract

Objective: To compare the effects of dual blockade with monotherapy angiotensin-converting-enzyme inhibitor and angiotensin-II receptor blocker in patients with hypertension due to unilateral renal artery stenosis.

Design: An open label, prospective, randomized crossover study.

Setting: A single center study in a primary teaching hospital. Twelve patients with angiographically proven unilateral renal artery stenosis and hypertension.

Intervention: In a crossover design, all patients were treated for three periods of eight weeks. After a run-in period, patients were randomized for either monotherapy enalapril or losartan, followed by a second eight-week period on the alternative monotherapy. At the end of the second eight-week period, dual therapy was given for eight weeks.

Results: The casual blood pressure on enalapril was 180±9 /92±4 mm Hg and on losartan 180±9/97±6 mmHg (both $P < 0.05$ compared to baseline). After dual therapy the blood pressure was 166±8/87±3 mm Hg ($P < 0.01$, for systolic BP, compared with baseline). The 24-hour blood pressures decreased in the same magnitude: from 166±9/88±4 mmHg on baseline, to 155±12/86±6 mmHg on enalapril, to 159±9/81±5 mmHg on losartan and to 148±8/83±3 mmHg on dual therapy ($P < 0.05$, compared to baseline). Serum creatinine and potassium remained stable during all three-treatment regimes.

Conclusion: Dual blockade of the RAAS by an angiotensin-converting-enzyme inhibitor and angiotensin-II receptor blocker was not superior compared to either monotherapy in patients with renovascular hypertension.

Introduction

Atherosclerotic renal artery stenosis is the most common cause of secondary hypertension, particular in older patients [1]. Blood pressure control is important to prevent both progressive target organ damage and progressive renal function loss in these patients [2]. Recent investigations have shown that revascularization procedures do not appear to be superior to medication in patients with renal artery stenosis [3, 4]. Therefore, pharmacological treatment plays a central role in blood pressure control in this population [5-8]. Angiotensin-converting-enzyme inhibitors effectively lower blood pressure in renovascular hypertension, but in many patients monotherapy is not sufficient to obtain normal blood pressure [9]. Several data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) by combined ACE-i and angiotensin-II- receptor blocker is more effective than either monotherapy in these patient categories [10-14]. So far, no studies addressed this issue in patients with ARAS, a condition that is frequently associated with resistance to antihypertensive therapy. Therefore, we studied the blood pressure response with monotherapy enalapril and losartan, respectively, in a short term, crossover study in a small group of patients with unilateral renal artery stenosis, as compared to the effect of combined blockade of both drugs.

Patients and Methods

Fifteen patients, nine male and six female (mean age 65 ± 8 yr) with renovascular hypertension due to URAS were recruited from the outpatient clinic of the Twenteborg Hospital Almelo. Renovascular hypertension was diagnosed based on angiographically proven URAS with more than 50% lumen reduction and/or an abnormal renal scintigraphy of the affected side. Hypertension was defined as a casual diastolic blood pressure greater than 95 mm Hg on two occasions in the run-in period. Before the trial, all patients had well-controlled blood pressures using ACE-i, ten patients also used diuretics and seven patients had at least triple therapy including a Beta-blocker. Exclusion criteria were severe cardiac or cerebrovascular disease and malignant hypertension. Serum creatinine had to be stable and below 150 µmol/l for at least 6 months. Written informed consent was obtained from all patients, and the ethical committee of the hospital approved the study.

Study design

The study was conducted according to an open label, prospective, crossover study design. All previous antihypertensive medications were withdrawn for at least one week. After discontinuation of medication, patients visited the outpatient clinic twice a week. For safety reasons, patients were allowed to start with the study medication when the diastolic blood pressure exceeded 115 mmHg. Median period without medication was 10 ± 3 days. After the baseline period, patients were randomized to start with monotherapy enalapril 20 mg bid or losartan 50 mg bid, for eight weeks followed by eight weeks on the other drug. After the 2 periods of 8 weeks monotherapy, all the patients received the combination of losartan and enalapril for 8 weeks in the same dosage. Patients visited the outpatient clinic at 4 weeks intervals, for measurement of blood pressure and laboratory measurements. Twenty-four hour blood pressure measurements were made at baseline and at the end of each treatment period.

Measurements

Blood pressure

Casual blood pressure was measured with a standard sphygmomanometer. The patients were required to remain in a sitting position for at least five minutes, after which three consecutive blood pressure measurements separated by one minute were made. Twenty-four hour blood pressure measurements were done with a Spacelabs 90207 device (Spacelabs, Ohio, USA). Measurements included twenty-four hour mean, diastolic and systolic blood pressure, daytime values (measured every 15 min from 7.00 to 22.00 h) and nighttime values (measured every 20 min from 22.00 to 7.00 h). If the number of readings was more than 80%, the measurement was noted as successful.

Renal function and serum electrolytes

Serum BUN, creatinine and electrolytes (potassium and sodium) were measured every four weeks and renal function was estimated by the Cockcroft formula [15].

Data analysis

Data are given as means and standard errors of the mean. Comparison of blood pressures and renal function were assessed using ANOVA test for repeated measurements (using SPSS 11.1 software, Gorinchem, the Netherlands). Correlation between individual

responses was calculated by means of Spearman rank test. A *P* value of < 0,05 was considered statistically significant.

Results

Three patients did not complete the trial (2 due to angina pectoris after withdrawal of their Beta blocker, and 1 patient developed a lung carcinoma in the first treatment period), the remaining 12 patients were able to complete the trial. Three patients refused to undergo 24-hour blood pressure measurements, so in 9 patients results for the 24-hour BP analysis were available. Group means are depicted in table 1. After discontinuation of the previous medication the casual blood pressure rose from 154±10/ 89±4 to 201±10/ 105±5 mmHg (*P*<0.001). After 8 weeks treatment with enalapril blood pressure decreased to 180±9/ 92±4 mmHg and after 8 weeks losartan to 180±9/ 97±6 mmHg. Combination therapy further decreased blood pressure to 166±8/ 87±3 mmHg (*P*< 0.05, compared with enalapril and losartan). Measurements of the 24-hour blood pressures showed a similar pattern, though the absolute values were lower. None of the measured blood pressures differed significantly, though a tendency for further lowering on combination therapy was noted (Table 1). Renal function remained stable under the three treatment modalities (Table 1) and serum potassium did not increase during dual blockade.

Table 1. Effects of treatment with enalapril, losartan and combination therapy on casual blood pressure, 24-hour blood pressure (n=9) and Cockcroft clearance in 12 patients with renovascular hypertension.

	Previous therapy	Base line	Enalapril	Losartan	Combination therapy
24 hour ABPM					
- Systolic BP (mmHg)		166 ± 9	155 ± 12	159 ± 9	148 ± 8[a]
- Diastolic BP (mmHg)		88 ± 4	86 ± 6	81 ± 5	83 ± 3
Mean BP (mmHg)		115 ± 5	110 ± 7	109 ± 5	107 ± 5
Casual BP					
- Systolic BP (mmHg)	154 ± 10[c]	201 ± 10	180 ± 9[a]	180 ± 9[a]	166 ± 8[a,b]
- Diastolic BP (mmHg)	89 ± 4[c]	105 ± 5	92 ± 4[a]	97 ± 6[a]	87 ± 3[a]
Creat Cl (ml/min)		72 ± 6	72 ± 6	74 ± 5	70 ± 6

ABPM, 24-hour ambulatory blood pressure; BP, blood pressure; Creat Cl, Cockcroft clearance. a = p < 0.05 versus baseline; b = p < 0.05 versus enalapril and losartan; c = p < 0.01 versus baseline

Discussion

To our knowledge this is the first study comparing the anti-hypertensive effects of monotherapy with an ACE-i or an ARB with dual therapy in patients with URAS. Our results showed beneficial effects of dual therapy compared to either monotherapy in patients with URAS, but only as regards to the casually measured blood pressure and not in the 24 hour-blood pressure measurements. So, the added effect of dual blockade, if anything, was modest in this study. Previous studies with different group of patients [10-14] suggest that dual therapy with an ACE-i and an ARB is more effective than monotherapy, though the findings are not uniform. Recently, the ONTARGET trial was published [16], where maximum dose of ramipril (10 mg per day) was compared with 80 mg of telmisartan and the combination of the two drugs in patients with vascular disease or high-risk diabetes. In this population, telmisartan was equivalent to ramipril. The combination of the two drugs was associated with more adverse events without an increase in benefit. This landmark study sheds light in how to interpret our data. It's a well known fact that patients with ARAS often have multiple comorbidities such as peripheral vascular disease [17] or coronary heart disease [18]. Therefore, optimal pharmacological treatment is essential. The STAR and ASTRAL trial [3, 4] have demonstrated that in patients with renal artery stenosis, stent placement compared with medical treatment had no clear effect on progression of impaired renal function. The study findings favor a conservative approach to patients with ARAS, focused on cardiovascular risk factor management and avoiding stenting. Following the ONTARGET trial, there is currently no evidence to treat patients with dual blockade and given that our data didn't show clear improvement of antihypertensive effects, there is no support to treat renal artery stenosis patients with dual blockade. Furthermore, the blood pressure in our patients was lower with their initial antihypertensive medication (10 with diuretic and 7 with triple therapy) suggesting that combination with another class of antihypertensive is better that dual blockade alone. Some limitations to our study must be considered. Mainly, for safety reasons, the washout period was very brief, and this may have induced bias in the efficacy of particularly the first monotherapy period, due to carry-over effect. Whereas monotherapy was randomized in a parallel fashion, dual blockade was always at the end of the study. Thus a time effect cannot be excluded. Secondly, the number of eligible patients was very small – with consequently a relatively low power to detect difference between the 3 regimens. Finally, doses were not titrated to a maximum effect.

These factors limit the possibility to draw definite conclusions about an added effect of the combination therapy ACE-i and ARB. However, the individual crossover design, starting with monotherapy, nevertheless allows relevant inferences. In conclusion: dual therapy with an ACE-i and an ARB in patients with renovascular hypertension, due to URAS, was well tolerated. The individual responses to monotherapy were concordant and the additive effect was modest and only significant for casually measured blood pressure.

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Chapter 5

Incidental renal artery stenosis is an independent predictor of mortality in patients with peripheral vascular disease

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Abstract

In patients with peripheral vascular disease (PVD) mortality is high. In this population renal artery stenosis (RAS) is a frequent incidental finding. RAS carries a high risk for mortality, but whether incidentally discovered RAS is a risk factor for mortality is unknown. The prognostic impact of incidental RAS for mortality was studied in 550 consecutive patients who underwent intra-arterial digital subtraction angiography (DSA) for PVD in our center between 1997 and 2000. In 491 patients (336 men, 155 women; mean follow-up 3.8 ± 1.9 years) the renal arteries were visualized and follow-up data were available. RAS (diameter reduction more than 50 %) was present in 26% of the patients. Mortality in the RAS group was 59% versus 28% in the non-RAS group (odds ratio 3.8; confidence interval 2.5 to 5.7, $P < 0.0001$). Diabetes, previous myocardial infarction, history of PVD, stroke and hypertension were more frequent in the RAS group; age was higher and GFR was lower in the RAS group. Thus, RAS was associated with elevated mortality and increased prevalence of cardiovascular risk factors. Cox-regression analysis showed that RAS was an independent predictor for mortality ($P = 0.005$), along with age, diabetes, smoking, previous myocardial infarction, history of PVD, and stroke. In patients who were evaluated for PVD by DSA mortality was high. Incidental RAS was a frequent finding and an independent predictor for mortality. Whether RAS is a marker for or, alternatively, a mediator of the poor prognosis and whether prognosis can be improved by specific intervention should be the subject of future prospective studies.

Introduction

In patients with peripheral vascular disease mortality is high [1-4], this is likely to be due to the clustering of cardiovascular risk factors in these patients. When renal function impairment is simultaneously present, mortality is even higher [5]. Renal artery stenosis is frequently encountered as an incidental finding in patients undergoing routine angiography for PVD, with a prevalence between 5 and 40% [6-8]. This corresponds to the high prevalence of RAS (5 to 20%) in patients who undergo routine coronary angiography [9,10]. Atherosclerotic RAS is associated not only with hypertension, ischemic nephropathy and cardiovascular disease [11,12], but also with a considerably increased mortality [13-15]. The impact of RAS as a risk factor for mortality was established mainly in populations that underwent a diagnostic work-up for hypertension and/or renal failure. Data in patients who underwent diagnostic cardiac catheterization simultaneously with an aortography [9,10] showed that incidental RAS can be an independent risk factor for mortality. Whether this holds also true for incidental RAS in PVD has not been established so far. We therefore investigated the prognostic impact of incidental RAS for mortality in consecutive patients who underwent intra-arterial digital subtraction angiography (DSA) for PVD in a single center between 1997 and 2000.

Materials and Methods

We reviewed a cohort of 550 consecutive patients who had clinically confirmed PVD by noninvasive examinations (ankle-brachial index or duplex Doppler of the lower extremities) and underwent angiography with the intention of surgical or radiological intervention from January 1997 to December 2000 in a single center, as judged by the vascular surgeons. Patients in whom the angiogram did not allow proper assessment of the renal arteries were excluded from the analysis. A single reviewer, blinded to patients' diagnoses and indications for the procedure, evaluated the angiograms for RAS. A diameter reduction of more than 50% was considered diagnostic for presence of RAS; severe stenosis was considered to be present when the stenosis exceeded 75% [10]. Clinical data were obtained from patient records and mortality data were obtained from the hospital information system.

Definitions

Hypertension was defined according to the 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension [16,17], prescription of antihypertensive medications, or a clinical history of hypertension. A patient was classified as having diabetes if there was a clinical history of diabetes or if the patient was taking insulin or oral antidiabetic agents. We used the abbreviated Modification of Diet in Renal Disease equation advocated in the Kidney Disease Outcomes Quality Initiative guidelines [18] to estimate glomerular filtration rate (GFR). These data are presented in the paper. In addition, we estimated GFR by the quadratic equation proposed by Rule *et al.* [19], because this equation is assumed to provide a better estimate of renal function in patients in whom renal function is normal or only mildly impaired. All analyses were also performed using estimated GFR by the latter equation; this did not alter the results (data not shown).

Baseline characteristics

Eight clinical variables were recorded at baseline (*i.e.*, time of angiography): Serum creatinine before angiography, history of myocardial infarction, history of stroke, diabetes (present or absent), smoking history (ever/stopped or never), history of prior PVD (*i.e.* previous treatment either conservative or not otherwise specified), history of hypertension and current BP at time of angiography.

Statistical analysis

Comparisons between groups (RAS *versus* non-RAS) on baseline variables were done using χ^2 test. Survival was assessed by Kaplan-Meier curves, and to test for independent predictors of mortality, we performed multivariate analysis using single-step Cox regression analysis. The renal function was classified according to the cutoffs recommended in the Kidney Disease Outcomes Quality Initiative criteria [18] for defining moderate (GFR 30-60 ml/min/1.73m2) and severe (GFR < 30 ml/min/1.73m2) renal function impairment. All statistical analyses were performed in SPSS 12.0 for Windows. Statistical significance was defined as a $P < 0.05$.

Results

From January 1997 to December 2000, 550 consecutive angiograms were performed in patients with all confirmed PVD. The renal arteries could be assessed in their entirety for RAS (diameter reduction >50% to 75% and ≥75%) in 499 angiograms. The reasons for incomplete visualization of the renal arteries were technical. Of the 499 assessable patients, eight could not be included because of incomplete clinical data. Atherosclerotic RAS was present in 129 (26%) of the 491 patients; of these patients, 35 (27%) had a luminal RAS of more than 75%, and 74 (57%) had a bilateral RAS.

Table 1. Characteristics of patients with and without RAS[a]

Characteristic	No RAS (n = 362)	RAS (n = 129)	P	OR (95% CI)
Age (yr; mean ± SD)	65 ± 11	72 ± 10	<0.0001	
Male gender (% [n])	70.4 (255)	81 (62.8)	0.108	
Mortality (% [n])	27.6 (100)	58.9 (76)	<0.0001	3.76 (2.47 to 5.71)
Systolic BP (mmHg; mean ± SD)	152 ± 26	153 ± 28	0.62	
Diastolic BP (mmHg; mean ± SD)	83 ± 13	83 ± 16	0.56	
History of hypertension (% [n])	53.9 (195)	71.3 (92)	0.001	2.10 (1.36 to 3.25)
History of diabetes (% [n])	27.1 (98)	39.5 (51)	0.01	1.74 (1.14 to 2.66)
History of myocardial infarction (% [n])	19.6 (71)	32.6 (42)	0.003	1.98 (1.26 to 3.11)
History of stroke (% [n])	14.9 (54)	22.5 (29)	0.049	1.66 (0.99 to 2.74)
History of smoking (% [n])	63.3 (229)	49.6 (64)	0.003	0.54 (0.36 to 0.81)
History of previous PVD (% [n])	30.7 (111)	45.0 (58)	0.003	1.85 (1.22 to 2.79)
GFR (ml/min per 1.73 m^2; mean ± SD)	79.7 ± 25.0	63.8 ± 26.2	<0.0001	

[a]CI, confidence interval; OR, odds ratio; PVD, peripheral vascular disease; RAS, renal artery stenosis.

Baseline characteristics of the population are presented in Table 1 and were divided according to presence or absence of RAS. Patients with RAS were significantly older and their mortality was significantly higher than in patients without RAS (59% and 28%, respectively; P<0.0001). In patients with RAS, the prevalence of several cardiovascular risk factors (hypertension, diabetes, previous history of PVD, myocardial infarction and stroke) was higher than in patients without RAS, but the proportion of smokers, remarkably, was lower in the group with RAS. As shown by the Kaplan-Meier survival curves in Figure 1, the estimated 5-year survival probability was 37% for patients with RAS as compared with 72% for patients without RAS (odds ratio of 3.76). Patients with moderate and severe renal function impairment were overrepresented among the patients with RAS as compared with the group without RAS (Table 2). Among patients with RAS ≥75% the majority had moderate or severe renal function impairment, whereas this amounted to approximately one-third of the patients with RAS <75% (Table 2). Mean GFR was 67.2 ± 25.4 ml/min for RAS <75%

versus 54.8 ± 26.4 ml/min for RAS ≥ 75% (*P* = 0.016). Therefore, RAS and its severity are associated with the severity of renal function impairment. The association of renal function and unilateral RAS *versus* bilateral RAS was NS (data not shown).

Table 2. Distribution of baseline GFR according to the presence or absence of RAS and the severity of RAS

	No RAS (n = 362)	RAS (n = 129)	P^a	RAS < 75% (n = 94)	RAS ≥ 75% (n = 35)	P^b
GFR > 60 ml/min	78.7% (285)	55.8% (72)	<0.0001	63.8% (60)	34.3% (12)	0.003
GFR 30 to 60 ml/min	20.7% (75)	35.7% (46)	0.001	29.8% (28)	51.4% (18)	0.023
GFR < 30 ml/min	0.6% (2)	8.5% (11)	<0.0001	6.4% (6)	14.3% (5)	0.153

[a]No RAS *versus* RAS.
[b]RAS <75% *versus* RAS ≥75%.

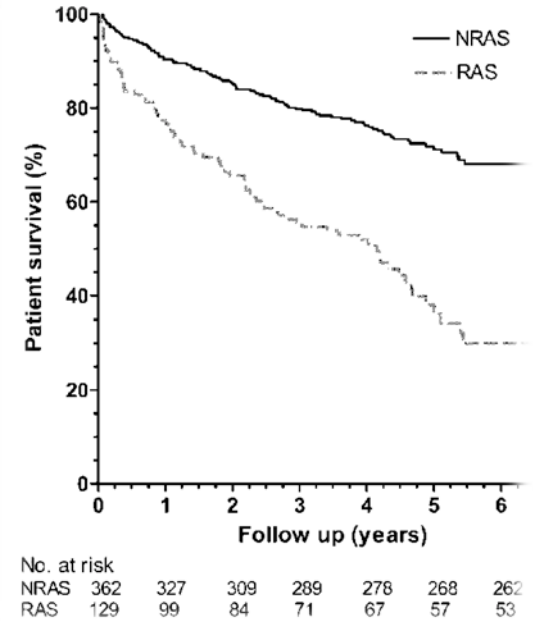

Figure 1. Kaplan-Meier survival plots for 491 patients with peripheral vascular disease, comparing outcome for those without renal artery stenosis (NRAS) and those with renal artery stenosis (RAS).

The crude mortality rates by absence or presence and severity of RAS is given in Table 3, showing significant effects of presence and severity of RAS on mortality, both for the population as a whole and after stratification of GFR in each of the various strata of GFR, *i.e.*, normal tot mildly impaired renal function (GFR >60 ml/min), moderately impaired renal function (GFR 30 to 60 ml/min) and severely impaired renal function (GFR <30 ml/min). Mortality was particularly high in patients with moderate and severe renal function impairment. Time-dependent survival by presence or absence of RAS, and by stratum of

renal function is shown as Kaplan-Meier curves in Figure 2. It shows that RAS and GFR <60 ml/min both were associated with worse survival, with the poorest survival in patients with both RAS and GFR <60 ml/min (overall log rank test χ^2 *P* <0.0001; group 1 *versus* group 2: *P*=0.0025; relative risk [RR] 1.89, 95% confidence interval [CI] 1.31-3.49); group 3 *versus* group 1 *P*<0.0001, RR: 2.44, 95% CI 1.92 to 5.41; group 4 *versus* group 1: *P*<0.0001, RR 4.61, 95% CI 2.92 to 22.8).

Table 3. Overall mortality and distribution of GFR according to presence or absence of RAS and severity of RAS

	No RAS (n = 362)	RAS < 75% (n = 94)	RAS ≥ 75% (n = 35)	*P* (ANOVA)
All patients	27.6% (100/362)	54.3% (51/94)	71.4% (25/35)	0.0001
GFR > 60 ml/min	23.9% (68/285)	45% (27/60)	58.3% (7/12)	0.0001
GFR 30 to 60 ml/min	41.3% (31/75)	64.3% (18/28)	72.2% (13/18)	0.017
GFR < 30 ml/min	50% (1/2)	100% (6/6)	100% (5/5)	0.047

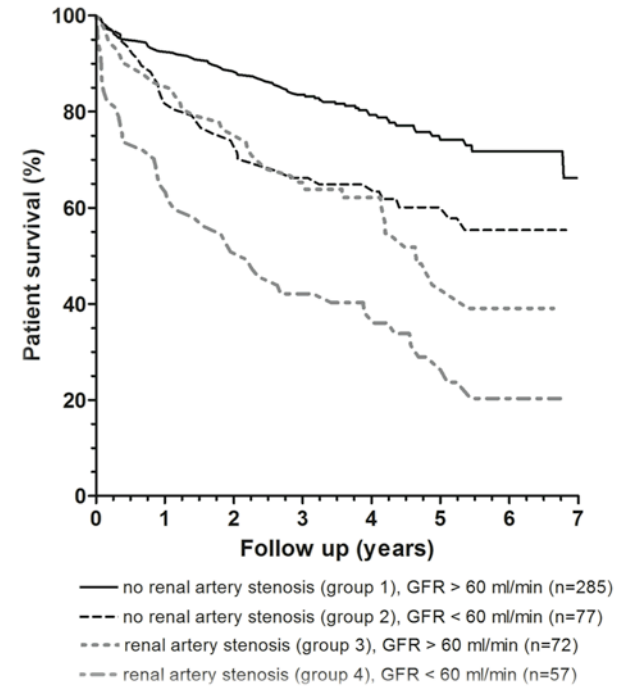

Figure 2. Kaplan-Meier survival plots for patients with PVD and GFR > 60 ml/min per 1.73 m^2 and GFR <60 ml/min per 1.73 m^2, comparing outcome for those without RAS and those with RAS.

The independent contribution of the various risk factors for mortality was assessed by Cox-regression analysis, as shown in Table 4. It shows first the crude model, in which the widely known cardiovascular risk factors age, diabetes, history of previous PVD, smoking,

previous myocardial infarction and previous stroke, were independent predictors for mortality. The contribution of stratum of renal function reached significance only for GFR <30 ml/min (P = 0.047). When the model was adjusted for presence of RAS, the contribution of class of renal function was attenuated, whereas RAS was an independent predictor for mortality (P = 0.005).

Table 4. Single-step Cox multivariate analysis of the predictors of mortality[a]

	HR (95% CI)	*P*
Crude analysis		
age	1.09 (1.07 to 1.11)	0.000
history of hypertension	1.13 (0.80 to 1.59)	0.492
history of diabetes	1.90 (1.36 to 2.65)	0.000
history of myocardial infarction	1.61 (1.15 to 2.26)	0.006
history of stroke	1.71 (1.19 to 2.46)	0.004
history of smoking	1.91 (1.34 to 2.73)	0.000
history of previous PVD	1.71 (1.23 to 2.39)	0.001
GFR > 60 ml/min		0.053
GFR 30 to 60 ml/min	0.87 (0.60 to 1.26)	0.453
GFR < 30 ml/min	1.95 (1.01 to 3.77)	0.047
Adjusted for RAS		
age	1.09 (1.07 to 1.11)	0.000
history of hypertension	1.11 (0.79 to 1.57)	0.547
history of diabetes	1.88 (1.35 to 2.62)	0.000
history of myocardial infarction	1.53 (1.09 to 2.15)	0.014
history of stroke	1.64 (1.14 to 2.37)	0.008
history of smoking	1.93 (1.35 to 2.76)	0.000
history of previous PVD	1.64 (1.18 to 2.29)	0.003
GFR > 60 ml/min		0.177
GFR 30 to 60 ml/min	0.86 (0.59 to 1.24)	0.417
GFR < 30 ml/min	1.60 (0.82 to 3.15)	0.171
RAS	1.62 (1.15 to 2.27)	0.005

[a]HR, hazard ratio.

Discussion

Our data confirm that incidental RAS is a frequent finding in patients evaluated for peripheral vascular disease by DSA. The main finding of our paper is that we demonstrated, for the first time, that RAS is an independent predictor of mortality in this population. Moreover, we found that incidental RAS was closely associated with the level of renal function. Remarkably, the prognostic impact of incidental RAS was true both in patients with normal or mild renal function impairment, and in patients with moderate to severe renal insufficiency.

The prevalence of incidental atherosclerotic RAS in our population was 26%, which is well within the range observed in other studies on PVD, in which prevalences ranged from 5

to 40% [6-8]. Prevalence obviously can be confounded by the definition used; our definition of RAS (a 50% reduction in renal artery lumen) is in line with similar studies on survival in coronary artery disease [9,10], and our cutoff for severe stenosis (≥75% luminal narrowing) is in accordance with the study described by Conlon *et al.* [10].

In patients with PVD, mortality is high. McKenna *et al.* [1] found a 5-year survival of 44% in patients with PVD (as demonstrated by an ankle-brachial index of <0.4) *versus* an 85% survival in patients without vascular disease. Criqui *et al.* [2] reported a 5-year survival of 70% in patients with symptomatic PVD *versus* 90% in normal individuals. When renal insufficiency was present concomitantly, mortality was even higher, with a 1-year survival rate of 56% for patients with a GFR <30 ml/min per 1.73 m^2 compared with 83% for patients with a GFR >60 ml/min per 1.73 m2 [5]. The overall mortality in our patients is in line with these studies, but our data also show that the subgroup with RAS has a prognosis that is considerably worse. Also, in patients with symptomatic RAS, mortality is increased, but the reported mortality rates are lower than in our patients with RAS. Isles *et al.* [14] reported a 5-year survival probability of 83% for patients with renovascular hypertension, and Wollenweber *et al.* [13] found a 5-year survival of 67% for patients with atherosclerotic renovascular disease *versus* 90% for the general population. A more recent study by Wright *et al.* [15] showed a mortality rate of 35.7% for patients with atherosclerotic renovascular disease using a mean follow-up of 27.7 months. Whereas a direct comparison is not warranted, our data nevertheless suggest that incidental RAS in patients with PVD carries a particularly poor prognosis, especially in patients with moderate to severe renal failure (of whatever cause).

What would be the implications of our findings? First, our study is the first to allow for mutual association between RAS, renal function impairment and mortality in patients with PVD. These data may provide a potential pathogenic link between the association of PVD and renal insufficiency [20] and the association between renal function impairment and increased mortality in patients with PVD as described by O'Hare *et al.* [5], respectively. Our data suggest that a considerable proportion of the presence of renal function impairment in PVD can be ascribed to the presence of RAS but do not allow a conclusive dissection as to which of the two is the main causal factor for mortality. It is remarkable in this respect that adjustment for RAS attenuated the impact of renal function in the multivariate model, but considering their close association, it presumably would be overly artificial to attempt to

disentangle their respective impact, so whether RAS is an independent causal factor remains hypothetical. In principle, RAS in itself can exerts deleterious pathophysiological effects by excess production of angiotensin II [21], which is a potent vasoconstrictor that has been implicated in the activation of cell proliferation systems [22]. High levels of angiotensin II are associated with left ventricular hypertrophy, endothelial dysfunction and target organ damage [23]. This pathway could explain, at least partially, the increased mortality in symptomatic atherosclerotic RAS. If this would be the case, it would be logical to assume that pharmacological blockade of the renin-angiotensin aldosterone system might have the potential to ameliorate the poor prognosis, but obviously this assumption would need empirical substantiation.

Second, our data suggest that incidentally found RAS can serve as a marker of a poor prognosis. When RAS is present, it is a strong marker of extended cardiovascular disease as suggested by the well-established clinical predictors of incidental RAS. Therefore, it could well be a marker of more extended coronary or cerebrovascular disease and thus related to increased mortality. In this perspective, it has been shown that in patients who undergo diagnostic cardiac catheterization simultaneously with an aortography, incidental RAS was an independent risk factor for mortality [9,10]. Moreover, the severity of RAS was related to mortality. In our study, however, no appropriate characterization of coronary or cerebrovascular disease was available, because the patients all were referred to the hospital by the general practitioner because of suspicion of PVD and were evaluated and treated by the vascular surgeon only. Therefore, a possible relationship between RAS and its severity and coronary artery disease cannot be made for our population.

As anticipated, several well-established clinical predictors of incidental RAS, namely older age [24-26], hypertension [24,25,27,28], impaired renal function [24,28], a history of coronary artery disease [9,10,24,26], and diabetes [25,27,28] were more prevalent in our group with RAS, with the exception, however, of a history of smoking [25,27]. This seeming discrepancy may be due to bias by indication, because the patients with RAS were older and had more symptomatic comorbidity, and therefore were more likely to have received previous advice to stop smoking. Whereas the difference in prevalence of risk factors may have contributed to the overall difference in mortality, the Cox regression analysis demonstrated the independent contribution of RAS.

The clinical implications of incidentally discovered RAS so far are uncertain. Studies on its natural history [6,15,29,30] reported that progression to end stage renal failure is rare [6,7]. From the perspective of preservation of renal function, therefore, revascularization is not recommended for patients with incidentally discovered RAS [6,7]. It may be worthwhile to refer these patients to the internist or cardiologist for a thorough screening for cardiovascular disease and for aggressive cardiovascular preventive therapy. It is known that aggressive treatment of hypertension and strict regulation of diabetes improves cardiovascular morbidity and mortality [31-33], and that an intensive lipid-lowering statin regimen can improve prognosis in high-risk populations [34].

Some limitations of our study should be considered. Because this was a retrospective *post hoc* analysis, we were not able to evaluate all of the renal arteries in the patients. In addition, all but eight patients were included in the follow-up. Unfortunately, the specific number of deaths due to cardiovascular problems is not known because cause of death was not specified in our patient data and our hospital information system was not linked to a national registry for death registration. All the angiograms were performed in the same center; as a result, it may influence the generalizability of our findings. However, all angiographies were analyzed by the same radiologist, who was blinded to patient diagnosis and indications, so there were no inter-observer variances. In the patient records, it was remarkable that hardly any of these patients were under medical supervision by an internist or a nephrologist. This may be because all our patients described were referred by general practitioners to the vascular surgeon. Our patients, therefore, may well be representative for those referred for angiography for evaluation for PVD. However, it may not be representative for the whole PVD population, because it is known that many patients with PVD go unrecognized in general practice [35].

Conclusion

Incidental RAS is a frequent finding in patients who are evaluated for PVD by DSA, and this finding predicts mortality independent of other risk factors. Therefore, risk assessment in patients who undergo angiography for PVD could be improved by consideration of the renal arteries. Future prospective studies should examine whether RAS is a marker or mediator of poor prognosis and whether prognosis can be improved by specific intervention or medical therapy.

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Chapter 6

Impact of incidental renal artery stenosis on long-term mortality in patients with peripheral arterial disease undergoing vascular procedure

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Abstract

Objective: In peripheral arterial disease (PAD) mortality is high. Incidental renal artery stenosis (RAS) is a predictor of mortality in PAD patients undergoing angiography. This might be relevant for risk-benefit assessment when vascular surgery is considered, both in terms of perioperative risk, and in terms of life expectancy.

Methods: We studied the prognostic impact of incidental RAS in 488 subjects (334 men, 154 women; mean follow-up 6.0 ±3.4 years) who underwent angiography for PAD in a single center between 1997 and 2000. Renal arteries were visualized and follow-up data concerning vascular procedures analyzed.

Results: RAS (diameter reduction >50 %) was present in 26%. Forty-six percent of study patients underwent a vascular procedure (85% vascular surgery, remainder underwent amputation). Patients that underwent vascular surgery had a better renal function at baseline, less history of stroke, and a larger proportion of smokers. Overall mortality was similar for patients that underwent surgery (54.5%) and those without surgery (49.6%). There was no difference in 90-day postoperative mortality for patients without or with RAS (7.2% vs 10.3%; NS). For subjects that underwent bypass surgery, long-mortality was substantially and significantly higher among those with RAS (65.1%) vs those without RAS (43.5%). On Cox regression analysis, age was the only independent predictor of 90 days postoperative mortality. The well-known cardiovascular risk factors of age, diabetes mellitus, history of prior peripheral vascular disease, smoking, prior myocardial infarction, prior stroke, and amputation, as well as presence of RAS, were independent predictors for overall mortality.

Conclusion: In PAD incidental RAS predicts long-term mortality independent of other risk factors. The elevated mortality is not due to a higher postoperative risk. Subjects presenting with PAD and RAS can therefore undergo vascular procedures with the same risk as other patients.

In patients with peripheral arterial disease, mortality is high [1-3] and is most likely related to the clustering of cardiovascular risk factors in these patients. When renal function impairment is simultaneously present, mortality is even higher [4]. Renal artery stenosis is frequently encountered as an incidental finding in patients undergoing routine angiography for PAD, with prevalence between 5 and 40% [5-7]. We have previously demonstrated that incidental RAS is an independent predictor of a substantially elevated mortality in PAD patients [6]. The hypothesis is that patients with incidental RAS have higher mortality due to higher postoperative risk. This might be relevant for risk-benefit assessment when vascular surgery is considered, both in terms of perioperative risk, and in terms of life expectancy. Therefore, we investigated the prognostic impact of incidental RAS for long-term mortality as well as perioperative mortality in a cohort of consecutive subjects who underwent intra-arterial digital subtraction angiography for PAD in a single center between 1997 and 2000, and were treated either conservatively or by vascular intervention, depending on clinical assessment.

METHODS

Design of the study. For the cohort of 550 consecutive patients described previously [6], with clinically confirmed PAD by noninvasive examinations (*i.e.*, ankle-brachial index or duplex ultrasound of the lower extremities), patient records were reviewed, and detailed additional data regarding vascular procedures were extracted. Briefly, these were subsequent patients, diagnosed between 1997 and 2000. For the current study, follow-up for mortality (in the previous report until 2004) was extended until January 1, 2008, amounting to a mean follow-up time of 6 years. All patients underwent angiography with the intention of surgical or radiological intervention from January 1997 to December 2000 in a single center, as judged by the vascular surgeons. Patients in whom the angiography did not allow proper assessment of the renal arteries were excluded from the analysis. A single reviewer (H.H.), blinded to patients' diagnoses and indications for the procedure, evaluated the angiograms for the presence of renal artery stenosis. A diameter reduction of >50% was considered diagnostic for the presence of RAS; severe stenosis was considered to be present when the stenosis exceeded 75% [8]. Clinical data, including surgical or radiological procedures, were obtained from patient records and mortality data (until January 1, 2008)

were obtained from the hospital information system. The Institutional Review Board approved this study.

Definitions. Hypertension was defined according to the 2007 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension [9], prescription of antihypertensive medications, or a clinical history of hypertension. A patient was classified as having diabetes if there was a clinical history of diabetes or if the patient was taking insulin or oral anti-diabetic agents. We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation advocated in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [10] to estimate glomerular filtration rate (GFR).

Baseline characteristics. Eight clinical variables were recorded at baseline (*i.e.*, time of angiography): the serum creatinine before angiography; a history of myocardial infarction; a history of stroke; diabetes mellitus (present or absent); smoking history (ever/stopped or never); history of prior PAD (*i.e.*, previous treatment either conservative or not otherwise specified); history of hypertension; and current blood pressure at time of angiography.

Vascular procedures. Vascular procedures were defined as either a surgical procedure (*i.e.*, primary vascular bypass operation or amputation) or endovascular treatment (*i.e.*, revascularization with primary percutaneous transluminal angioplasty).

Statistical analysis. Comparisons between groups (renal artery stenosis vs nonrenal artery stenosis) on baseline variables were performed using Pearson χ^2test. Survival was assessed by Kaplan-Meier curves, and to test for independent predictors of mortality, multivariate analysis was performed using single-step Cox regression analysis. The renal function was classified according to the cut-offs recommended in the KDOQI criteria [10] for defining moderate (GFR 30-60 ml/min/1.73m^2) and severe (GFR < 30 ml/min/1.73m^2) renal function impairment. All statistical analyses were performed in SPSS 14.0 for Windows SPSS, Chicago, Ill). Statistical significance was defined as a *P* value <.05.

RESULTS

From January 1997 to December 2000, 550 consecutive angiograms were performed in patients, all with confirmed PAD. The renal arteries could be assessed in their entirety for renal artery stenosis (diameter reduction **>**50%-75% and **≥**75%) in 499 angiograms. The

reasons for incomplete visualization of the renal arteries were technical. Of the 499 evaluable patients, 11 patients could not be included because of incomplete clinical data. Atherosclerotic renal artery stenosis was present in 128 (26%) of the 488 patients; of these patients, 35 (27%) had a luminal renal artery stenosis of more than 75%, and 73 (57%) had a bilateral renal artery stenosis.

Baseline characteristics of the population are presented in Table I, by a break-up according to whether or not surgery was performed. Of the 224 patients that underwent a vascular procedure, 190 (85%) had vascular surgery; the remainder underwent an amputation. Patients that underwent vascular surgery had a better renal function at baseline, less history of stroke, and a larger proportion of smokers, suggesting impact of patient selection for surgery. Long-term mortality was similar for patients that underwent surgery (54.5%) and those without surgery (49.6%).

Table I. Baseline clinical characteristics of 488 patients with and without vascular operation

Characteristic	*No operation (n = 264)*	*Operation (n = 224)*	P	*Odds ratio (95% confidence interval)*
Age (years; mean ± SD)	66.4 ± 11.5	65.7 ± 11.2	.54	
Male gender (% [n])	63.3 (167)	74.6 (167)	.07	
Overall mortality (% [n])	49.6 (131)	54.5 (122)	.29	1.21 (0.85-1.74)
RAS (% [n])	26.5 (70)	25.9 (58)	.88	0.97 (0.65-1.45)
GFR (mL/min per 1.73 m^2; mean ± SD)	71.4 ± 25.0	80.3 ± 26.4	<.0001	
- GFR in patients with no RAS	76.0 ± 23.6	83.7 ± 25.3	.003	
- GFR in patients with RAS	58.4 ± 24.1	70.6 ± 27.4	.008	
History of hypertension (% [n])	58.7 (155)	57.8 (129)	.85	0.97 (0.67-1.39)
History of diabetes (% [n])	29.5 (77)	32.1 (72)	.53	1.13 (0.77-1.67)
History of myocardial infarction (% [n])	20.8 (55)	25.4 (57)	.23	1.30 (0.85-1.98)
History of stroke (% [n])	20.1 (53)	13.4 (30)	.05	0.62 (0.38-1.003)
History of smoking (% [n])	57.5 (145)	67.1 (147)	.033	1.51 (1.03-2.20)
History of previous PAD (% [n])	31.4 (83)	37.5 (84)	.16	1.31 (0.90-1.90)

GFR, Glomular filtration rate; *PAD*, peripheral arterial disease; *RAS*, renal artery stenosis.

Table II shows the baseline characteristics of patients who underwent percutaneous transluminal angioplasty (PTA) compared with vascular surgery. There was no difference in short-term mortality; only long-term mortality was slightly elevated in patients who underwent vascular surgery. There was no difference in the renal function or the other risk factors between the groups. Patients with RAS were older and had a higher prevalence of cardiovascular risk factors (Table III). In Table IV, mortality data are presented by a break-up by presence or absence of RAS, for patients that underwent surgery and those who had not. Among the patients that underwent surgery, mortality was extremely high for those with RAS and similar for those with or without RAS that underwent amputation. For subjects that

underwent bypass surgery, mortality was substantially and significantly higher among those with RAS (65.1%) versus those without RAS (43.5%). There were no differences, however, in 90-day and 1-year postoperative mortality for patients with RAS as compared with no RAS, and there was no difference in mortality between patients with unilateral RAS versus bilateral RAS (Table V).

Table II. Baseline clinical characteristics of 366 patients who underwent PTA or vascular operation

Characteristic	*PTA (n =142)*	*Operation (n = 224)*	P	*Odds ratio (95% confidence interval)*
Age (years; mean ± SD)	64.7 ± 12.5	65.7 ± 11.2	.44	
Male gender (% [n])	61.3 (87)	74.6 (167)	.007	
Overall mortality (% [n])	43.7 (62)	54.5 (122)	.044	1.54 (1.01-2.36)
90-day postoperative mortality (% [n])	4.2 (6)	8.0 (18)	.151	1.98 (0.77-5.12)
1-year postoperative mortality (% [n])	11.3 (16)	14.3 (32)	.41	1.31 (0.69-2.49)
RAS (% [n])	22.5 (32)	25.9 (58)	.47	1.20 (0.73-1.97)
GFR (mL/min per 1.73 m^2; mean ± SD)	75.2 ± 23.5	80.3 ± 26.4	.06	
- GFR in patients with no RAS	78.5 ± 22.7	83.7 ± 25.3	.86	
- GFR in patients with RAS	63.6 ± 22.8	70.6 ± 27.4	.22	
History of hypertension (% [n])	55.6 (79)	57.8 (129)	.68	1.09 (0.72-1.67)
History of diabetes (% [n])	27.1 (38)	32.1 (72)	.31	1.27 (0.80-2.03)
History of myocardial infarction (% [n])	20.4 (29)	25.4 (57)	.27	1.33 (0.80-2.21)
History of stroke (% [n])	14.1 (20)	13.4 (30)	.85	0.94 (0.51-1.74)
History of smoking (% [n])	64 (87)	67.1 (147)	.54	1.15 (0.73-1.80)
History of previous PAD (% [n])	28.2 (40)	37.5 (84)	.066	1.53 (0.97-2.41)

GFR, Glomular filtration rate; *PAD*, peripheral arterial disease; *PTA*, percutaneous transluminal angioplasty; *RAS*, renal artery stenosis.

Table III. Baseline clinical characteristics of patients with and without renal artery stenosis

Characteristic	*No RAS (n = 360)*	*RAS (n = 128)*	P	*Odds ratio (95% confidence interval)*
Age (years; mean ± SD)	64 ± 11	71 ± 10	<.0001	
Overall mortality (% [n])	44.2 (159)	73.4 (94)	<.0001	3.50 (2.24-5.49)
History of hypertension (% [n])	53.8 (193)	71.1 (91)	.001	2.12 (1.37-3.27)
History of diabetes (% [n])	27.5 (98)	39.8 (51)	.009	1.75 (1.15-2.67)
History of myocardial infarction (% [n])	19.4 (70)	32.8 (42)	.002	2.02 (1.29-3.18)
History of stroke (% [n])	15.0 (54)	22.7 (29)	.048	1.66 (1.00-2.75)
History of smoking (% [n])	65.9 (228)	51.2 (64)	.004	0.54 (0.36-0.82)
History of previous PAD (% [n])	30.6 (110)	44.5 (57)	.004	1.83 (1.21-2.76)
GFR (mL/min per 1.73 m^2; mean ± SD)	79.6 ± 24.7	63.9 ± 26.2	<.0001	

GFR, Glomular filtration rate; *PAD*, peripheral arterial disease; *RAS*, renal artery stenosis.

Table IV. Long-term mortality and postoperative mortality for patients with or without vascular surgery according to the presence or absence of renal artery stenosis

	No RAS (n = 360)	*RAS (n = 128)*	P
No operation (n = 264)	4.7% (79/194)	74.3% (52/70)	<.0001
All operation (n = 224)	48.2% (80/166)	72.4% (42/58)	.001
- Bypass operation (n = 190)	43.5% (64/147)	65.1% (28/43)	.013
- Amputation (n = 34)	84.2% (16/19)	93.3% (14/15)	.412
90-day postoperative mortality (% [n])	7.2 (12)	1.3 (6)	.45
1-year postoperative mortality (% [n])	13.3 (22)	17.2 (10)	.56

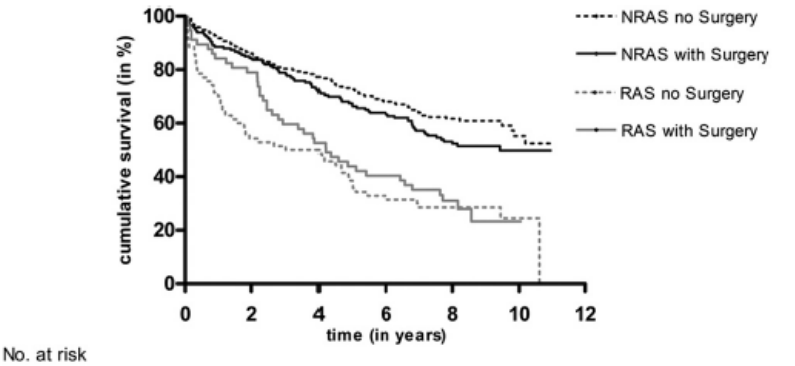
RAS, Renal artery stenosis.

Table V. Long-term mortality and postoperative mortality for patients with or without vascular surgery according to the presence of unilateral or bilateral renal artery stenosis

	Unilateral RAS (n = 55)	*Bilateral RAS (n = 73)*	P
No operation (n = 70)	82.4% (28/34)	66.7% (24/36)	.133
All operation (n = 58)	71.4% (15/21)	73% (27/37)	.90
- Bypass operation (n = 43)	70.6% (12/17)	61.5% (16/26)	.54
- Amputation (n = 15)	75% (3/4)	100% (11/11)	.086
90-days postoperative mortality (% [n])	9.5 (2)	10.8 (4)	.88
1-year postoperative mortality (% [n])	19 (4)	16.2 (6)	.46

RAS, Renal artery stenosis.

As shown by the Kaplan-Meier survival curves in the Fig, the estimated 5- and 10-year survival probability for patients who did not undergo a vascular procedure was 72% and 55%, respectively, for patients without RAS as compared with 36% and 24%, respectively, for patients with RAS. The estimated 5- and 10-year survival probability for patients with a vascular procedure in the group without RAS was 66% and 50%, respectively, versus 42% and 23%, respectively, in the group with RAS (*P* <.0001).



No. at risk

NRAS no Surg	194	167	149	132	120	107
NRAS with Surg	166	139	119	105	87	83
RAS no Surg	70	38	34	22	20	17
RAS with Surg	58	45	30	23	18	14

Fig. Kaplan-Meier survival plots for patients with peripheral arterial disease with and without surgery, comparing outcome for those without renal artery stenosis (*NRAS*) and with renal artery stenosis (*RAS*).

The independent contribution of the various risk factors for 90-day postoperative mortality and long-term mortality were assessed by Cox regression analysis, as shown in Table VI and VII, respectively. For the 90-day postoperative mortality, age was the only independent predictor (*P* = .001). The well-known cardiovascular risk factors age, diabetes,

history of prior peripheral vascular disease, smoking, prior myocardial infarction, prior stroke, and amputation, as well as presence of RAS, were independent predictors for long-term mortality.

Table VI. Single-step Cox multivariate analysis of the predictors of 90-day postoperative mortality

	P	*Hazard ratio (95% confidence interval)*
Age	.001	1.09 (1.35-1.16)
History of hypertension	.46	1.39 (0.58-3.31)
History of diabetes	.72	1.18 (0.47-2.98)
History of myocardial infarction	.23	1.68 (0.72-3.88)
History of stroke	.43	1.50 (0.55-4.10)
History of smoking	.11	2.23 (0.84-5.91)
History of previous peripheral arterial disease	.21	1.74 (0.74-4.13)
Amputation	.31	1.79 (0.58-5.49)
PTA vs vascular bypass operation	.53	1.34 (0.50-3.83)
Glomerular filtration rate	.72	0.99 (0.98-1.02)
Renal artery stenosis	.93	1.04 (0.43-2.50)

PTA, Percutaneous transluminal angioplasty.

Table VII. Single-step Cox multivariate analysis of the predictors of long-term mortality

	P	*Hazard ratio (95% confidence interval)*
Age	.000	1.08 (1.06-1.10)
History of hypertension	.418	1.12 (0.85-1.48)
History of diabetes	.000	1.74 (1.31-2.30)
History of myocardial infarction	.002	1.55 (1.67-2.06)
History of stroke	.001	1.65 (1.22-2.25)
History of smoking	.000	1.73 (1.28-2.33)
History of previous peripheral arterial disease	.003	1.50 (1.15-1.97)
Amputation	.002	2.01 (1.29-3.12)
Glomerular filtration rate	.553	1.00 (0.99-1.01)
Renal artery stenosis	.024	1.39 (1.04-1.84)

DISCUSSION

In our previous study, we demonstrated that the mortality in patients with PAD is extremely high, especially in patients with concomitant incidental RAS and PAD. As previously demonstrated, incidental RAS is an independent predictor of long-term mortality in patients with PAD [6]. In this study, we have examined the contribution of the perioperative mortality on the total (5- and 10-year) mortality. In contrast to our hypothesis

or previous ideas [11], this mortality was not influenced by the operative procedures, irrespective of the patient had a RAS or not. The 90-day and 1-year postoperative mortality was not significantly different in patients with and without RAS. In terms of life expectancy, patients with incidental RAS have higher mortality in comparison to patients without RAS; however, this is not due to postoperative short (90 days) or midterm (1 year) mortality.

The association between renal function and increased mortality in patients with PAD undergoing lower extremity bypass surgery has previously been described in this journal by O'Hare *et al.* [12] and Owens *et al.* [4]. The first study found that patients receiving dialysis have a high incidence of amputation within 1 year of lower extremity revascularization that is not explained by a higher prevalence of demographic characteristics and comorbid conditions. The second study demonstrated that in their cohort of 456 subjects, patients with more severe renal insufficiency had significantly higher mortality and lower amputation-free survival following lower extremity revascularization. The detrimental effects of reduced renal function are profound and begin well before the onset of dialysis. The overall5-year survival in this cohort was 43%. This is comparable to ours, namely 42% in patients with RAS after a vascular procedure. One may deduce from our data that the increased mortality in the two above-mentioned studies is due to poor prognostic impact caused by incidental RAS. In contrast to the previously depicted studies, renal function was not a prognostic marker for mortality in our cohort. Patients with PAD who underwent vascular operation had better renal function compared with those who were not operated (Table I). The patients with PAD who did not undergo vascular surgery had comparable kidney function to those who underwent PTA (Table II). The question arises how this is to be explained. One can hypothesize that patients with the worst renal function had severe inoperable vascular lesions and thus operation was deemed too risky. In this respect, patients with RAS who went through amputation had the lowest estimated glomerular filtration rate (eGFR; 60.2 ± 18.2 mL/min/1.73m^2). Another explanation may be preoperative selection bias by the initial physicians who determined whether the patient should be operated or not, based on renal function. Nevertheless, our data give us insight in the combined occurrence of RAS and renal function impairment as tools for preoperative risk-benefit assessment. Despite the high mortality associated with incidental RAS and renal insufficiency, they are not the cause of short- or long-term postoperative mortality. It may

therefore be anticipated that all patients with surgical indication for vascular operation should be operated upon.

Some limitations of our study should be considered. Because this was a retrospective post hoc analysis, all liabilities associated with the retrospective nature of the study apply. The fact that 90-day postoperative mortality was not significant may be due to underpowering of this study to really discriminate in short-term mortality. However, as already mentioned, the primary aim was to evaluate the long-term mortality in patients with PAD and incidental RAS. Regrettably, nonfatal perioperative events and medication use were not recorded. The medication use especially can be of importance, since the data of this study were obtained starting back in 1997. In the past, many patients with PAD were not treated as aggressively as today, such as standard with statins, angiotensin-converting enzyme inhibitors, or rigorous antiplatelet therapy. With the knowledge of the medication use, it was possible to discriminate whether the patients in our study were treated according to the standards of current practice. Furthermore, we cannot rule out that more favorable patients were selected for surgery.

CONCLUSION

Incidental RAS predicts long-term mortality independent of other risk factors. RAS is a strong marker of a poor prognosis, manifested in increased mortality and inoperability in patients with PAD. Consequently, risk assessment in patients who undergo angiography should include visualizing the renal arteries and measurement of renal function. Despite the elevated mortality in subjects with RAS, the postoperative risk does not contribute to the amazing high total mortality, and therefore patients with PAD and RAS should not be withheld from vascular surgery.

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Chapter 7

Summary and general discussion

In this thesis we addressed the clinical implications of atherosclerotic renal artery stenosis and the potential therapeutic options in patients with renovascular hypertension and patients with peripheral arterial disease. The studies illustrate the changing perspective on the role of the stenosis as such, that has traditionally been regarded as a *causal* factor of renovascular hypertension, with apparently clear causal intervention possibilities for hypertension and renal function. However, this concept is increasingly challenged. First, by the variable results of patency restoration of the renal artery on blood pressure and renal function, and, second, by the increasing recognition of the fact that ARAS is often an *incidental* finding in patients that undergo angiography for disorders other than hypertension such as PAD. Remarkably, presence of ARAS as an *incidental* finding has substantial prognostic impact. So, in the context of *incidental* renal artery stenosis "coincidental" is not the same as *innocent* in the end.

Treatment of renovascular disease

Renal vascular intervention has historically played a central role in the treatment of renovascular hypertension, based on the assumption that the renal artery stenosis was the driving and maintaining force underlying the renovascular hypertension. With the technical advances in endovascular intervention, even complex atherosclerotic lesions can be treated in many patients. In the medical world, the enthusiasm for such interventions has been great for a long time, as experimental data suggested that this was the solution for the Goldblatt phenomenon, thus providing a causal therapy for renovascular hypertension, as a secondary form of hypertension, that should therefore be the preferred treatment, with the theoretical potential to alleviate the need for lifelong treatment with blood pressuring lowering drugs. However, as we described in ***chapter 2***, it has become increasingly clear that the effect of anatomically successful intervention on blood pressure and/ or renal function is not readily apparent for all patients. For blood pressure control, there seems little improvement in comparison to medical therapy alone. As for renal function, the results are even more disappointing. Whereas PTRA can favorably affect overall renal function, such an effect is usually absent in subjects with stable renal function, or in those in whom irreversible parenchymal damage is present, as suggested by stable chronic moderate to severe renal function impairment or presence of albuminuria before intervention. Such a clinical setting

should therefore prompt for caution in decision-making on renal vascular intervention. Current data, including the latest trials, STAR [1] and ASTRAL [2], indicate that improvement of kidney function after renal vascularization (on top of standard medical therapy) is not to be expected for patients with normal to mildly impaired stable renal function, especially not in those with unilateral renal artery stenosis. However, in selected cases, as shown by a recent study [3], revascularization can result in renal function improvement, particular in patients with a rapid deterioration of renal function in the year or months before intervention, in whom renal function is nevertheless still relatively well preserved at the time of intervention.

In the past decades, substantial progression has been made in the pharmacological treatment of patients with renovascular hypertension. In this respect the introduction of classes of antihypertensive medication blocking the renin-angiotensin-aldosterone system has been of landmark importance, and the same is true for availability of powerful lipid-lowering drugs such as statins. By these advancements in drug treatment, it became possible to treat these patients more aggressively, both with respect to blood pressure as such and with respect to dyslipidemia as a factor driving progressive atherosclerotic disease.

The improvement in potency of pharmacological intervention may be one of the reasons for lack of superiority of vascular intervention over conservative therapy. Restenosis, after initially successful vascular intervention might be an alternative explanation, with potentially different clinical consequences. No systematical assessment of the occurrence of restenosis after patency restoration, and its association with responses of blood pressure and renal function was available so far. Therefore, we examined the relationship between success of angioplasty on patency of the renal artery (***chapter 3***) by a systematic assessment of one-year renovascular patency after PTA irrespective blood pressure. Although the immediate patency in our group was good, with 96% patency in patients with URAS (23/24) and 75% in patients with BIRAS (12/16), after 1 year more than half of the patients (22/40) had restenosis of their renal arteries. Unlike current concept, in our patients with unilateral renal artery stenosis, the relationship between restoration of vessel patency and BP response is not one-to-one. After 1 year, 5 out of 10 patients with a patent renal artery after PTA, the hypertension returned, whereas 5 out of 14 patients with restenosis of the renal artery had improved BP compared to baseline. Thus, taken together, in these patients there was no association whatsoever between patency and blood pressure response! For patients with

bilateral renal artery stenosis, the results of the data are more difficult to interpret, because in patients with bilateral lesions the elevated blood pressure may be maintained by either of the renal arteries. Thus, after patency restoration a stenotic contralateral renal artery can be the main factor driving the elevated BP. Since in our group of patients with bilateral stenosis, a contralateral stenosis inaccessible to intervention was present in 7 patients, this could be involved in the eventual BP effect.

Taken together, our findings support the increasing body of evidence showing that ARAS is not the main pathogenetic factor in the elevated blood pressure in the majority of ARAS patients with hypertension. Alleviation of the renal artery stenosis may be mainly a "cosmetic" anatomical procedure, without affecting the true pathogenetic forces driving the hypertension, namely renal damage due to ischemia of the stenotic kidney, resulting in progressive renal fibrosis and atrophy in the post-stenotic kidney accompanied by hypertensive nephropathy in the contralateral kidney. Given that renovascular hypertension is associated with activation of the RAAS as a possible mechanism underlying the elevated blood pressure, we investigated in ***chapter 4*** more complete blockade of the RAAS with an ACE-i and ARB dual blockade versus monotherapy on the blood pressure response in patients with URAS. As expected, the response of blood pressure was equal in the groups treated with monotherapy ACE-i or ARB. The combined effect showed as anticipated further decrease in blood pressure in absolute values. However with measurement of the 24-hour blood pressures it did not reach significance compared to monotherapy alone. Furthermore, the casual blood pressure in our patients was lower with their initial antihypertensive medication (more than half of the patient had triple therapy) than with combined therapy with ACE-i and ARB – making the results difficult to interpret.

- Current data indicate that improvement of kidney function after renal vascularization (on top of standard medical therapy) is not to be expected for patients with normal to mildly impaired stable renal function, especially patients with unilateral renal artery stenosis.
- There is no relationship between anatomical effects on patency of the renal artery by PTA, and the BP response, or recurrence of the stenosis and the return of hypertension.

- Dual blockade of the RAAS by an angiotensin-converting-enzyme inhibitor and angiotensin-II receptor blocker is not superior compared to either monotherapy in patients with renovascular hypertension.

Incidental renal artery stenosis

With the emergence of angiography as a common procedure for detecting coronary as well as peripheral arterial disease, incidental RAS is an often-encountered condition, varying from 5-40%. In the current literature the impact of renal artery stenosis as a risk factor for mortality is well recognized, mainly based on populations that underwent a diagnostic work-up on clinical suspicion of renovascular hypertension. The prognostic impact of incidental RAS however was not clear. In ***chapter 5*** we demonstrated that incidental RAS is a frequent finding (26%) in patients who are evaluated for PAD by DSA and, for the first time, that incidental RAS predicts mortality independent of other well known classical risk factors, with twofold mortality in RAS versus non RAS. Moreover, we found that incidental RAS was closely associated with the level of renal function in this population, which allowed us to look at the mutual association among renal artery stenosis, renal function impairment, and mortality in patients with PAD. When renal artery stenosis is present, it is a strong marker of extended cardiovascular disease as supported by the association with well-established clinical predictors of incidental RAS [4-7]. As incidental RAS emerges as a "byproduct" of a routine diagnostic procedure, it might be useful to integrate this independent risk indicator in the risk-assessment of patients with PAD.

To be of help in clinical decisions, it would be useful to know whether this mortality is due to an increased (peri-) operative risk related to the surgical vascular procedure or merely a representation of the overall high-risk profile of these patients. In ***chapter 6*** therefore we examined the contribution of the peri-operative mortality on the total (5- and 10-year) mortality. In contrast to our hypothesis the elevated mortality was not due to an increased peri-operative risk. The 90 days- and 1 year postoperative mortality was not significantly different in patients with and those without RAS. In terms of life expectancy, patients with incidental RAS have higher mortality in comparison to patients without RAS, however this is not due to postoperative short (90 days) or mid-term (1 year) mortality.

Consequently, risk assessment in patients who undergo angiography with the intention of vascular intervention should include visualizing the renal arteries and measurement of renal function. This allows us to better identify the patients with the highest mortality risk, in whom integrated vascular care (*i.e.* by an internist or cardiologist); with a full work-up for vascular risk profile should be prompt. It is known that aggressive treatment of hypertension and strict regulation of diabetes improve cardiovascular morbidity and mortality [8-13] and that an intensive lipid-lowering statin regimen can improve prognosis in high-risk populations [14-17]. Despite the elevated mortality in subjects with RAS, the peri- and postoperative risk does not contribute to the strikingly high total mortality and therefore patients with PAD and renal artery stenosis should not be withheld from vascular surgery when indicated.

- Patients with peripheral arterial disease and incidental renal artery stenosis have a high mortality rate compared to those without renal artery stenosis.
- Incidental renal artery stenosis is a frequent finding in patients who are evaluated for peripheral arterial disease by DSA, and this finding predicts mortality independent of other risk factors.
- The elevated mortality in patients with peripheral arterial disease and incidental renal artery stenosis is not due to a higher postoperative risk. Subjects presenting with peripheral arterial disease and renal artery stenosis can therefore undergo vascular procedures with the same risk as other patients.

From Goldblatt phenomenon to generalized vascular disease: the changing perspective of atherosclerotic renal artery stenosis.

From the first reports by Harry Goldblatt in 1934 [18] until to date, researchers have tried to find the “holy grail” for the treatment of renovascular hypertension. At first this seemed very straightforward, since obstruction of the renal artery is the cause of the hypertension, and accordingly relief of the stenosis by renal artery intervention could alleviate the stenosis, keep the artery patent and consequently cure the hypertension. As such, renovascular hypertension has long been in the textbooks as one of the main forms of secondary hypertension, for which a causal treatment was available. Now, decades later and facing the outcome of the recent STAR [1] and ASTRAL [2] trials, we have come to the

conclusion that the reality is more complex than in the first reports described by Goldblatt and colleagues, and that restoration of renal artery patency not always leads to a persisted reduction of blood pressure or improvement of renal function.

To understand the discrepancy between the Goldblatt phenomenon and the frequent lack of success in patients with ARAS, two important mechanisms should be considered. The first one is the potential of reduced renal perfusion pressure to induce a rise in systemic blood pressure by renin release and the consequent activation of angiotensin II. The ensuing cascade includes sympathetic nerve activation and recruitment of endothelium-based proliferation systems, only some of which are reversible upon restoring renal perfusion [19]. Inflammatory and pro-fibrogenic pathways become activated during sustained renal ischemia and perpetuate irreversible renal damage. These factors often lead to tubulo-interstitial scarring and loss of glomerular filtration over time. In this phase, restoring renal artery perfusion usually no longer induces meaningful recovery of function since the impairment of renal function in this stage reflects late, structural effects of sustained renal ischemia, rather than a reversible hemodynamic impairment. Second, it is important to realize that atherosclerotic narrowing of the renal artery is usually not an isolated phenomenon, but part of a progressive process of generalized atherosclerosis. This is supported by multiple observations where ARAS is found together with coronary artery disease [5, 20], carotid artery stenosis [21, 22] and in patients with peripheral arterial disease [23-25]. As discussed in ***chapter 5 and 6*** of this thesis, incidental RAS is associated with increased prevalence of well-established risk factors such as diabetes mellitus, hypertension, coronary and cerebrovascular disease. Hence, the presence of renal artery stenosis is a strong marker of extended generalized atherosclerotic cardiovascular disease and the increased mortality found in these patients reflects their extensive cardiovascular burden. Consequently, revascularization of the ARAS alone will not alter the risk of cardiovascular morbidity and mortality.

So where do we go from here? It must be concluded that the Goldblatt phenomenon, which is one of the most studied models of hypertension, holds true for patients with fibromuscular disease, where alleviation of the renal artery stenosis, in an otherwise healthy vascular bed, cures the hypertension. In patients with ARAS, this is only true for selected cases and the most consistent predictor of benefit regarding both blood pressure and recovery of kidney function has been the rate of change of renal function up to the point of

diagnosis and revascularization [3, 26-28] that can be taken as a clinical indicator of the (lack of) chronicity of the post-stenotic renal damage. For that reason, our primary focus in patients encountered with ARAS is optimal treatment of generalized atherosclerosis according to the current guidelines. In addition, and not yet based on guidelines, currently new treatment modalities are being developed such as catheter-based renal denervation, which has shown its effectiveness in patients with treatment-resistant hypertension [29, 30]. As already mentioned, sympathetic nerve activation plays an important role in the rise and maintaining of elevated systemic blood pressure in patients with ARAS. Currently, this relatively new technique has only been applied in "normal" renal arteries. One can hypothesize to combine the dilatation or stenting of the renal artery stenosis with renal denervation in the contralateral kidney to ensure optimal treatment of the hypertension. Apart from all this, the greatest challenge at this moment remains to select the individual patient who is likely to benefit from renal artery revascularization.

To date, most imaging procedures concentrate specifically upon the anatomic severity and approachability of the ARAS, whereas functional characterization, such as renography with/without ACE-i, and renal vein catheterization has largely been abandoned due to lack of predictive power. While the anatomical characteristics are important, they are evidently not sufficient to predict the outcome of renal revascularization. Further work is needed to develop diagnostic tools that can identify renal parenchyma at true risk of "ischemic injury" and to identify when kidney function can be (or can no longer be) improved with renal revascularization. Until then, clinicians face the important task to weigh the pros and cons of renal artery intervention in the context of the available evidence each time ARAS is encountered in the individual patient.

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Chapter 8

Nederlandse samenvatting

In dit proefschrift wordt de klinische betekenis onderzocht van *atherosclerotisch nier arterie stenose* (***ARAS***) en de eventuele behandel mogelijkheden bij patiënten met *renovasculaire hypertensie* en *perifeer arterieel vaatlijden* (PAV). De studies laten zien dat de rol van nier arterie stenose, dat van oudsher wordt beschouwd als oorzaak (***causale factor***) van renovasculaire hypertensie met een duidelijk aangrijpingspunt voor behandeling aan het veranderen is. Aan dit concept wordt namelijk steeds meer getwijfeld.

In de eerste plaats door de wisselende resultaten van het *dotteren* van de nier arterie stenose op de bloeddruk en nierfunctie. Anderzijds doordat steeds vaker bij toeval (***incidenteel***) een nier arterie stenose wordt gevonden bij patiënten die een *angiografie* ondergaan in verband met perifeer vaatlijden. Opmerkelijk is dat deze bij toeval gevonden nier arterie stenose, een voorspellende waarde heeft op de overleving van patiënten. Derhalve betekent incidenteel nier arterie stenose niet altijd dat het onschuldig is.

Atherosclerotisch nier arterie stenose (ARAS) = vernauwing van de nierslagader door aderverkalking.
Renovasculaire hypertensie = hoge bloeddruk en vermindering van nierfunctie veroorzaakt door vernauwing van de nierslagader.
Perifeer arterieel vaatlijden (PAV) = vernauwing van de bloedvaten in de benen wat vaak gepaard gaat met pijn tijdens het lopen; in volksmond ook wel “etalage benen genoemd”.
Dotteren= open maken of wijder maken van een bloedvat door middel van het opblazen van een ballon in het bloedvat.
Angiografie = onderzoek van een bloedvat.

In hoofdstuk 2 worden de onderzoeken beschreven die tot nu toe zijn uitgevoerd naar het effect van dotteren van de nier arterie stenose op de bloeddruk en nierfunctie. Uit de onderzoeksresultaten komt naar voren dat het effect op verbetering van de bloeddruk klein is, ondanks een succesvolle dotter procedure. Verbetering van de nierfunctie na het (beter) doorgankelijk maken van de nier arterie (boven op standaard medicatie) wordt niet verwacht bij patiënten met normale tot matig gestoorde nierfunctie. Dit geldt vooral voor patiënten met enkelzijdige nier arterie stenose.

Patency = mate van geopend: meer dan 70% vernauwing is ernstig en minder dan 50 % vernauwing is niet belangrijk.

In hoofdstuk 3 wordt gekeken waarom het bloeddruk verlagend effect na een dotter procedure tegenvalt. We hebben dit gedaan door de relatie te onderzoeken tussen een succesvolle dotter ingreep en de *patency* van de nierarterie. Hoewel de onmiddellijke patency goed was (90 %), had na 1 jaar meer dan de helft van de patiënten bewezen opnieuw een stenose. Tevens konden we geen relatie vinden tussen de bloeddruk respons na 1 maand, na 1 jaar en de patency van de nier arterie. Met andere woorden, patiënten die geen nier arterie stenose meer hadden, hadden soms weer een hoge bloeddruk en vice versa.

renine-angiotensinesysteem: hormoon systeem wat in de nier geactiveerd wordt bij patiënten met een nier arterie stenose en zorgt voor bloeddruk stijging.

In hoofdstuk 4 wordt bij patiënten met een enkelzijdige nier arterie stenose, het bloeddruk verlagend effect vergeleken van 2 medicijnen afzonderlijk (enalapril en losartan) versus de combinatie van beide. De gebruikte medicijnen zorgen voor bloeddruk daling door een remmende werking op het *renine-angiotensinesysteem*. Beide medicijnen alleen gaven hetzelfde bloeddruk dalend effect, de combinatie gaf nog een verdere daling, echter was dit niet belangrijkverschillend tijdens de 24-uurs bloeddruk registratie.

Hoofdstuk 5 beschrijft de resultaten van 550 patiënten met PAV die een angiografie hebben ondergaan. Incidentele nier arterie stenose met een vernauwing van meer dan 50% kwam in 26% van de gevallen voor. Sterfte in de groep met nier arterie stenose was 59% vergeleken met 28% in de groep zonder nier arterie stenose. De traditionele risico factoren voor hart en vaat ziekten kwamen tevens vaker voor bij patiënten met nier arterie stenose. Incidentele nier arterie stenose was een onafhankelijke voorspeller voor sterfte, net als leeftijd, suikerziekte, roken en patiënten die een hartinfarct dan wel hersenberoerte hebben gehad.

In hoofdstuk 6 wordt tot slot de bijdrage van sterfte rond de operatieperiode op de lange-termijn sterfte onderzocht (5- en 10-jaarssterfte) in patiënten met PAV en nier arterie stenose. De sterfte was vergelijkbaar voor patiënten die een vaatoperatie hebben

ondergaan (54.5%) vergeleken met patiënten die niet werden geopereerd (49.6%). Er was 90 dagen na de operatie geen verschil in sterfte tussen de patiënten zonder en met nier arterie stenose. Wel hadden de patiënten met nier arterie stenose die geopereerd waren significant hogere lange-termijn sterfte (65.1%) vergeleken met patiënten zonder een nier arterie stenose (43.5%). Leeftijd was de enige voorspeller voor sterfte 90 dagen na de operatie. Zoals verwacht was incidentele nier arterie stenose wel een onafhankelijke voorspeller voor sterfte in het algemeen bij onze patiënten.

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List of abbreviations

ACE-i: angiotensin –converting-enzyme inhibitors

ARAS: atherosclerotic renal artery stenosis

ARB: angiotensin-II receptor blockers

ASTRAL trial: Angioplasty and STent for Renal Artery Lesions

BIRAS: bilateral renal artery stenosis

BP: blood pressure

CORAL trial: Cardiovascular Outcomes in Renal Atherosclerotic Lesions

DRASTIC trial: Dutch Renal Artery Stenosis Intervention Cooperative

DSA: digital subtraction angiography

EMMA trial: Essai Multicentrique Medicaments vs Angioplastie

FMD: fibromuscular dysplasia

GFR: glomerular filtration rate

MDRD: Modification of Diet in Renal Disease

NITER: Nephropathy Ischemic Therapy

NS: not significant

PAD: peripheral arterial disease

PTRA: percutaneous transluminal renal angioplasty

PTRAS: percutaneous transluminal renal angioplasty plus stenting

PVD: peripheral vascular disease

RAAS: renin-angiotensin-aldosterone system

RAS: renal artery stenosis

SNRASCG—Scottish and Newcastle Renal Artery Stenosis Collaborative Group

STAR trial: STent placement in patients with Atherosclerotic Renal Artery

Stenosis and Impaired Renal Function

URAS: unilateral renal artery stenosis